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Use of the FebriDx point-of-care test for the exclusion of SARS-CoV-2 diagnosis in a population with acute respiratory infection during the second (COVID-19) wave in Italy

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\textbf{A B S T R A C T}

\textbf{Objective:} Evaluate the real-world accuracy of Myxovirus resistance protein A (MxA) detected by the rapid, point-of-care FebriDx test during the second-wave pandemic in Italy in patients with acute respiratory infection (ARI) and a clinical suspicion of COVID-19.

\textbf{Design and methods:} Prospective, observational, diagnostic accuracy study whereby hospitalized patients with ARI were consecutively enrolled in a single tertiary care center in Italy from August 1, 2020 to January 31, 2021.

\textbf{Results:} COVID-19 was diagnosed in 136/200 (68.0%) patients and Non-COVID-19 was diagnosed in 64/200 (32.0%) patients. COVID-19 patients were younger and had a lower Charlson comorbidity index compared to Non-COVID-19 patients (p < 0.001). Concordance between FebriDx, MxA and rt-PCR for SARS-CoV-2 (gold standard) was good ($k = 0.93$, 95\% CI 0.87–0.99), Overall sensitivity and specificity were 97.8\% [95\% CI 93.7–99.5] and 95.3\% [95\% CI 86.9–99.0\%], respectively. FebriDx demonstrated a negative predictive value of 95.3\% (95\% CI 86.9–99.0) for an observed disease prevalence of 68.8\%.

\textbf{Conclusions:} FebriDx MxA showed high diagnostic accuracy to identify COVID-19 and could be considered as a real-time triage tool to streamline the management of suspected COVID-19 patients. FebriDx also detected bacterial etiology in Non-COVID-19 patients suggesting good performance to distinguish bacterial from viral respiratory infection.

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\textbf{Introduction}

SARS-CoV-2 infection is widespread around the world and is causing an overwhelming rate of contagion, hospital admissions and death. Coronavirus disease 2019 (COVID-19) poses a great challenge to infection prevention efforts in a hospital setting. A prompt diagnosis properly allocates the patient in a dedicated area, reducing the risk of nosocomial transmission. The gold standard for the diagnosis is detection of viral RNA by nucleic acid amplification technologies (NAATs) (usually a real time polymerase chain reaction (rt-PCR) performed on a suitable respiratory sample: nasopharyngeal (NP) swab, sputum, bronchoalveolar lavage (BAL) (ECDC, 2020). However, the decision to place a patient in a COVID-19 or Non-COVID-19 area is usually made before the result of the rt-PCR, which could take several...
hours. Molecular point-of-care testing (POCT) for COVID-19 may give faster indications about the correct patient destination, mitigating the risk of contagion among COVID-19 negative patients and unrecognized positive patients in a hospital setting or among healthcare personnel. In this perspective, rapid antigen tests for COVID-19 offer results in 10–30 min, and at low cost. Recently, the U.S. FDA authorized an antigen test as a fully at-home diagnostic for SARS-CoV-2 infection (Diao et al., 2021; ECDC, 2020). Alternative diagnostic solutions may help the clinician in the correct and rapid classification of patients with suspected COVID-19 prior to or when a pathogen specific test result is not available in time to make clinical decisions. Amongst the new applications for consideration is FebriDx (Lumos Diagnostics, Sarasota, Florida, US), a rapid, qualitative immunoassay test designed to test for viral or bacterial respiratory infection through the detection of both C-reactive protein (CRP) and Myxovirus resistance protein A (MxA) from a fingerstick blood sample (Self et al., 2017; Shapiro et al., 2018).

CRP is a nonspecific, acute-phase protein predominantly produced by the liver in response to inflammatory cytokines, such as IL-6 that are upregulated in response to acute inflammation and infection (Dahler-Eriksen et al., 1999; Diederichsen et al., 2000). MxA is exclusively induced by type I interferon (IFN) as a crucial part of specific immune response to a wide range of viral infections (Zav’yalov et al., 2018).

As such, the detection of elevated MxA by FebriDx is considered a “pan-viral” test that identifies the presence of active pathogens of the most common acute respiratory viral etiologies and remains low in bacterial infections or non-infectious conditions. Thus, FebriDx may triage patients at the initial visit and a negative result could play a role in excluding a SARS-CoV-2 infection (Clark et al., 2020; Karim et al., 2020). The diagnostic performance of FebriDx has been evaluated in single center studies in the UK during the first wave (March–April 2020) of the COVID-19 pandemic, showing high accuracy in the identification of COVID-19 hospitalized patients (Clark et al., 2020; Karim et al., 2020). This is the first diagnostic accuracy study to be conducted in Italy during the second wave of the COVID-19 pandemic which occurred during a time when other respiratory viruses (e.g., influenza) were expected to be prevalent in our setting. Therefore, the study aims to test the real-world accuracy of FebriDx during the second-wave pandemic in Italy in recently febrile patients with acute respiratory infection (ARI) and a clinical suspicion of COVID-19.

**Methods**

**Sample size**

To estimate a sensitivity point estimate of 85% with a 95% confidence interval, assuming a prevalence of COVID-19 hospitalized patients of around 30%, 164 patients were required. We increased these numbers to 200 to achieve an 80% chance of obtaining enough cases.

**Study design, setting and ARI definition**

This prospective diagnostic accuracy study aimed to assess the sensitivity, specificity, positive and negative predictive value of FebriDx MxA in patients with suspected COVID-19 as compared to Severe Acute Respiratory Syndrome Coronavirus-2 reverse transcriptase polymerase chain reaction (RT-PCR). Patients hospitalized at the tertiary care Careggi University Hospital in Florence, Italy with acute respiratory infection (ARI) were consecutively enrolled between August 1, 2020 to January 31, 2021. All patients included had a nasopharyngeal swab collected and tested for SARS-CoV-2 RT-PCR prior to admission. Participants were admitted to either the COVID-19 or Non-COVID-19 area according to the result of the molecular RT-PCR test. Non-COVID-19 patients were enrolled in four different medical departments while COVID-19 patients were admitted to the Infectious Diseases Department. FebriDx was performed at the time of enrollment and within 72 h of the NP swab collection for molecular testing of SARS-CoV-2.

**Inclusion criteria**

Hospitalized participants were prospectively included according to the following inclusion criteria: i) age ≥18 years old, ii) presence of ARI iii) consent to participate. Patients were not eligible for inclusion if any of the following criteria were met: i) chronic therapy with interferon ii) recent vaccination with live-attenuated virus vaccine (within the last 30 days) or iii) unwilling or unable to consent to participate.

**Definitions**

ARI was defined as at least one record of fever (body temperature ≥37.5 °C) in the last 72 h and at least one of the following symptoms: sore throat, persistent cough (with or

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**Figure 1.** FebriDx Result Interpretation.
Left: Control (blue) and MxA (middle, red) lines (response: viral positive). Middle: Control, MxA, CRP (top, gray) lines (response: viral positive). Right: Only control line (response: negative). Myxovirus resistance protein A (MxA). C-reactive protein (CRP).
without sputum), dyspnea, shortness of breath in the last seven days and/or a radiological image compatible with pulmonary inflammation. A high-dose steroids dose was defined as a dose >2 mg/kg or a total of >20 mg/day for 2 weeks or more. Patients were categorized as a COVID-19 case or Non-COVID-19 case according to the SARS-CoV-2 molecular test result. A COVID-19 case was defined as detection of SARS-CoV-2 by molecular test on a nasopharyngeal swab or BAL based on the first result within 72 h of the admission, while a Non-COVID-19 case was defined by an alternative final diagnosis and the absence of a single or repeated SARS-CoV-2 detection by molecular testing during the hospitalization.

Procedure and data collection

The FebriDx POC test generates results in the form of the presence or absence of three lines, assessed by visual inspection. From the bottom the first bar represents the control line (blue), MxA (middle, red) and CRP (top, grey). Intensity of the colors is linked to the blood amount of these proteins (Figure 1). Thresholds of detection are 20 mg/L for CRP and 40 ng/mL for MxA. To reduce the potential variability in interpretation, all investigators involved in the study were trained for a proper execution and interpretation of the test. Each FebriDx result was read independently by two investigators, and if there was disagreement on the results this was further adjudicated by a third investigator. In case of an indeterminate test, this was repeated. Routine SARS-CoV-2 molecular testing on NP swabs collected in universal transport media (UTM) was performed using various CE marked- tests for SARS-CoV-2 detection, including the Aptima® SARS-CoV-2 Assay (Hologic), the Xpert® Xpress SARS-CoV-2 assay (Cepheid), the SimplexaTM COVID-19 assay (Diasorin) or the AllplexTM SARS-CoV-2 Assay (Seegene). The latter system was used also with

Table 1
Baseline demographics and clinical characteristics in all patients, COVID-19 positive patients and COVID-19 negative patients according to the molecular testing for SARS-CoV-2 result from respiratory specimen.

|                          | All patients (%) (N = 200) | COVID-19 (%) (N = 136) | Non-COVID-19 (%) (N = 64) | p Value |
|--------------------------|-----------------------------|------------------------|---------------------------|---------|
| Gender                   |                             |                        |                           |         |
|  Cis-gender man           | 123 (61.5)                  | 83 (61.1)              | 40 (62.5)                 | 0.977   |
|  Cis-gender woman        | 74 (37.0)                   | 51 (37.5)              | 23 (35.9)                 |         |
|  Transgender man          | 3 (1.5)                     | 2 (1.5)                | 1 (1.6)                   |         |
| Median Age in years at study entry, [IQR] | 66 [52–80] | 61 [50–74.5] | 79 [65.5–85.5] | <0.001 |
| Median CCI               | 3 [1–5]                     | 2 [1–4]                | 5 [3–6.5]                 | <0.001 |
| Any corticosteroids therapy 72 h prior to FebriDx, (%) | 123 (61.5) | 91 (66.9) | 32 (50.0) | 0.022 |
| Any antibiotics therapy 7 days prior to FebriDx, (%) | 63 (31.5) | 47 (34.6) | 16 (25.0) | 0.175 |
| FebriDx Results. No (%)  |                              |                        |                           |         |
|  MxA with or without CRP (Viral) | 136 (68.0) | 133 (97.8) | 3 (4.7) |         |
|  CRP only (Bacterial)     | 56 (28.0)                   | 3 (2.2)                | 54 (84.4)                 |         |
|  CRP with or without MxA  | 151 (75.5)                  | 94 (69.1)              | 57 (89.1)                 |         |
|  Negative (control line only) | 9 (4.5) | 2 (1.5) | 7 (10.9) |         |
| Median Procalcitonin (ng/mL), [IQR] | 0.12 [0.06–0.27] | 0.09 [0.06–0.15] | 0.6 [0.18–1.83] | <0.001 |
| Median white blood cell (× 10^9/L), [IQR] | 7.4 [5.3–10.1] | 6.3 [4.7–8.3] | 10.7 [8.4–14.4] | <0.001 |
| Bacterial isolation from respiratory sample* | 8 (4.0) | 2 (1.47) | 6 (9.4) | <0.001 |
| Legionella urinary antigen |                             |                        |                           |         |
|  Present                 | 6 (3.0)                     | 0                      | 6 (9.4)                   |         |
|  Not performed           | 60 (30.0)                   | 54 (39.7)              | 6 (9.4)                   |         |
| Pneumococcal urinary antigen |                             |                        |                           |         |
|  Present                 | 19 (9.5)                    | 10 (7.3)               | 9 (14.1)                  | <0.001 |
|  Not performed           | 59 (29.5)                   | 54 (39.7)              | 5 (7.8)                   |         |
| Blood culture            |                             |                        |                           | 0.096   |
|  Positive                | 14 (7.0)                    | 6 (4.4)                | 8 (12.5)                  |         |
|  Not performed           | 13 (6.5)                    | 10 (7.4)               | 3 (4.7)                   |         |
| Median days between the symptom onset and FebriDx, [IQR] | 6 [3–9] | 7 [5–10] | 3 [2–5] | <0.001 |
| High dose steroids or immunosuppressive therapy |                             |                        |                           | 0.367   |
| Final disposition (%)    |                             |                        |                           | 0.369   |
|  Hospital discharge      | 168 (84.0)                  | 51 (79.7)              | 117 (86.0)                |         |
|  Deceased                | 15 (7.3)                    | 5 (7.8)                | 10 (7.3)                  |         |
|  Transferred to another hospital | 17 (8.5) | 9 (6.6) | 8 (12.5) |         |

CCI: Charlson comorbidity index; MxA: Myxovirus resistance protein A; CRP: C-reactive protein; High dose steroids defined as dose >2 mg/kg or a total of >20 mg/day for 2 weeks or more.
*Bronchoalveolar Lavage (BAL) performed on 13 unique patients. Sputum collected on 7 unique patients. BAL and sputum collected on 2 unique patients. COVID-19 BAL: 1 Klebsiella pneumoniae; COVID-19 Sputum: 1 Staphylococcus aureus; Non-COVID-19 BAL: 1 S aureus, 1 Rhinovirus, 1 Pneumocystis jirovecii; Non-COVID-19 sputum: 2 Pseudomonas aeruginosa, 1 Acinetobacter baumannii.
respiratory specimens other than nasopharyngeal swabs. Results of the FebriDx tests were recorded in a dedicated database along with the following variables: date of birth, gender, comorbidities, concomitant medications, onset of symptoms in days, hospitalization and discharge date, final diagnosis, real-time cycle threshold (CT) counts (when available). With rT-PCR systems which detected more than one target gene, the lowest CT value was considered regardless of the nature of the detected targets. Procalcitonin (ng/mL), white blood cell count and CRP (mg/L) were recorded on the day the FebriDx was performed (± 1 day).

Ethics

Local Ethics Committees (17524/CAM_BIO) approved the study and the data collection. All patients provided written or verbal informed consent to use their data for research purposes. The study was conducted in agreement with the ethical principles of the Declaration of Helsinki.

Statistical analysis

Descriptive analysis was employed to illustrate population characteristics. Categorical variables were analyzed using Chi Squared/Fisher’s exact test and continuous variables with the Kruskal–Wallis test. FebriDx results were compared to SARS-CoV-2 rT-PCR, which served as the reference method. The agreement between FebriDx MxA and the reference method tests was calculated using the unweighted Cohen’s Kappa. Simple measures of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and likelihood ratios were calculated for FebriDx MxA detection of patients with COVID-19. Confidence intervals for sensitivity, specificity, and predictive values were calculated using the binomial exact method. Statistical analyses were conducted with Stata 14 (StataCorp, College Station, TX, USA).

Results

Enrollment took place from August 1, 2020 to January 31, 2021 and included 200 sequentially enrolled patients, of which 136 (68.0%) met the diagnostic criteria for COVID-19 and 64 (32.0%) were diagnosed as Non-COVID-19. Significant differences were noted between the two groups at the time of admission (Table 1). Patients with a COVID-19 diagnosis were younger (61 years [IQR 50–74] vs. 79 years [IQR 65–85]; p < 0.001) and had a lower Charlson comorbidity index (CCI) compared to Non-COVID-19 patients (2 [IQR 1–4] and 5 [IQR 3–6], respectively; p < 0.001). The median levels of procalcitonin and white blood cells were higher in Non-COVID-19 patients and the median days between the onset of symptoms and FebriDx testing was shorter in the Non-COVID-19 cohort (3 [IQR 2–5] and 7 [IQR 5–10], respectively). Serum CRP results were available for 184 out 200 patients: 49 out 64 (76.5%) in the Non-COVID-19 group and 135 out of 136 (99.3%) in COVID-19. The median baseline CRP was higher in Non-Covid (98 mg/L [IQR 39–191] compared to COVID-19 patients (47 mg/L [IQR 19–87]; p < 0.001). Using the thresholds of detection <20 mg/L, the concordance between serum CRP and FebriDx CRP was moderate (κ 0.53, 95% CI 0.40–0.67). No differences in final disposition (discharge, deceased or transferred to another hospital) were observed between the two groups (Table 1). Concordance between FebriDx MxA and COVID-19 definition was good (κ 0.93, 95% CI 0.87–0.99). Overall sensitivity and specificity were 97.8% (95% CI 93.7–99.9%) and 95.3% (95% CI 86.9%–99.0%), respectively (Table 2). Negative predictive value for FebriDx was determined to be 95.3% (95% CI 86.9–99.0) at a time when the observed prevalence was 68%. In 3 COVID-19 cases we observed a negative MxA (Table 3). CT counts were available for 37 out of 136 patients (27.2%). The median CT value was 22 [IQR 19–25]. The highest CT value in which MxA was also detected was 35. As for three COVID-19 cases non-detected by the MxA, the CT value was available for two and was 18 and 38, respectively. Overall, 14 patients (7.0%) were on high-dose steroids or immunosuppressive agents at the time of the enrollment with no difference between the groups (p=0.367) (Table 1).

Among Non-COVID-19 patients, 29 out 64 (45.0%) had a bacterial isolation (6 from BAL/sputum, 6 resulted positive to

| Table 2 | Measures of diagnostic accuracy of FebriDx MxA for identification of COVID-19, compared to the reference standard of positivity by molecular testing for SARS-CoV-2 genome. (n = 200). |
|---------|----------------------------------------------------------------------------------|
| n/n     | Value                             | 95% Confidence interval          |
| Prevalence | 136/200                             | 68%                             | 61.0–74.4% |
| Negative predictive value | 61/64                             | 95.3%                            | 86.9–99.0% |
| Positive predictive value | 133/136                           | 97.8%                            | 86.9–99.0% |
| Sensitivity | 133/136                           | 97.8%                            | 93.7–99.5% |
| Specificity | 61/64                             | 95.3%                            | 86.9–99.0% |
| Likelihood ratio (+) | –                                  | 20.9                             | 6.91–63 |
| Likelihood ratio (–) | –                                  | 0.23                             | 0.01–0.71 |

MxA: Myxovirus resistance protein A.

| Table 3 | Clinical and demographic characteristics of discordant pairs between MxA and molecular testing for SARS-CoV-2 results. |
|---------|-------------------------------------------------------------------------------------------------------------------------------------|
| Gender   | Age | Country of birth | CCI | PCT ng/mL | CRP mg/L | Days of onset of symptoms | High dose steroids or immune suppressive therapy | rT-PCR Cycle threshold | Final diagnosis                     |
| COVID-19 case and MxA not detected | 1 | Cis gender man | 29 | Peru | 0 | NA | 16 | 7 | No | – | SARS-CoV-2 pneumonia |
| 2 | Cis-gender man | 50 | Peru | 1 | 15.8 | 337 | 4 | No | – | SARS-CoV-2 pneumonia |
| 3 | Cis-gender woman | 66 | Italy | 3 | 0.33 | 142 | 11 | Yes | 38 | SARS-CoV2 pneumonia and myelofibrosis |
| Non-COVID-19 case and MxA detected | 4 | Cis-gender woman | 82 | Italy | 7 | 0.09 | 85 | 4 | No | – | Rhinovirus Pneumonia |
| 5 | Cis gender woman | 92 | Italy | 7 | 2.52 | 7 | 7 | No | – | Pneumonia | *
| 6 | Cis gender woman | 28 | Romania | 1 | 0.20 | <5 | 4 | No | – | Lupus |

CCI: Charlson comorbidity index; CRP: C-reactive protein; CT: Real-time-PCR cycle threshold; High dose steroids defined as dose >2 mg/kg or a total of >20 mg/day for 2 weeks or more; MxA: Myxovirus resistance protein A; PCT: procalcitonin.

* Viral identification by a polymerase chain reaction-based diagnostic panel not performed.
legionella urinary antigen, 9 resulted positive to pneumococcal urinary antigen and 8 had positive blood culture).

**Discussion**

In this real-life study we found an optimal concordance between FebriDx MxA and rt-PCR for SARS-CoV-2 during the second wave of the pandemic in Italy. MxA is a marker produced by the host as a response to a pan-viral infection. MxA is not specific for SARS-CoV-2; subsequently, the high specificity and PPV found in this study reflect the low prevalence of other respiratory viruses circulating during the study, such as influenza. The PPV could therefore drop, as the prevalence of COVID-19 decreases. On the other hand, as reported by Clark et al., we also found FebriDx to have both high sensitivity and NPV for ruling out COVID-19 in symptomatic patients (Clark et al., 2020). Therefore, as PPV decreases during times of low disease prevalence, it is expected that the NPV will increase, meaning that a negative FebriDx MxA will remain a useful rule out test even in a low-prevalence scenario.

In our clinical setting FebriDx could be introduced to streamline the intake selection process of emergency department, helping in cohorting decisions. Based on the high NPV, FebriDx could avoid an unintended exposure of Non-COVID-19 patients being cohabited in a COVID-19 area and prioritize confirmatory testing among FebriDx viral positive patients. As recently reported, during the SARS-CoV-2 pandemic the activity of influenza and most other respiratory pathogens decreased due to multiple (known and still unknown) possible reasons like temporary lockdowns, use of face-masks, social distancing, hand hygiene and reduced travel (Olsen et al., 2020). In this epidemiological scenario, a positive result of MxA detected by FebriDx also permits one to rule-in a COVID-19 diagnosis. The specificity and sensitivity found in this study are slightly higher compared to pre-COVID-19 literature on FebriDx when studied to differentiate between bacterial and viral infections. However, it must be specified that our study aim and the included population were different. Primarily, we intended to test FebriDx ability in discriminating between COVID-19 and Non-COVID-19 recently febrile symptomatic hospitalized patients, whereas the studies conducted in pre-COVID-19 were mainly comprised of both afebrile and febrile patients enrolled from an outpatient setting. The higher diagnostic performance noted in our study may be attributable to the increase of inflammatory response, and thus host response markers such as CRP and MxA, and may account for the improved diagnostic accuracy seen in our study. That said, our findings are similar to other studies conducted during the COVID-19 pandemic which included a similar patient population (Clark et al., 2020; Karim et al., 2020).

The manufacturers of FebriDx state the test is intended for use in patients who have had respiratory symptoms for less than or equal to 7 days, and up to 14 days in patients with suspected COVID-19. In agreement with Clark et al. we found a MxA detection in COVID-19 patients beyond this period. In contrast to previous studies where patients on immunosuppressive therapy or systemic corticosteroids were considered non-eligible, our study included both immunocompetent and immunocompromised patients to reflect a real-world clinical setting. In our cohort, home treatment with steroids within 72 h prior to hospital admission was frequent and their use seemed to not interfere with MxA detection. A sub-analysis of immunocompromised patients or patients taking high-dose steroids found that MxA was detected in 7 out 8 COVID-19 patients regardless of immunocompetency. In the immunocompromised case non-detected by the MxA, the CT value was 38. The high CT value may have played an important role in addition to the immunosuppression status (Table 3). This data should be carefully considered and further analyzed in other studies due to some caveats that can affect the CT value, in particular those related to the amplification technique and to the different timing in which the samples were taken as the viral load changes during the infection phase (Rao et al., 2020; Zacharioudakis et al., 2020). As an ancillary finding, we observed that in Non-COVID-19 patients, almost half of the cases could be traced back to a bacterial etiology, confirming the good performance of FebriDx in distinguishing bacterial from viral pneumonia. Finally, we found a moderate agreement between serum CRP and FebriDx CRP. This value may be underestimated as serum CRP may not have been collected on the same day as a ± 1 day shift from the FebriDx. When the bacterial stimulus which causes increased production of CRP completely ceases, such as after initiation of an antibiotic, the circulating CRP concentration falls rapidly at almost the rate of plasma CRP clearance (by half approximately every day) (Pepys and Hirschfield, 2003). Without complete bacterial stimulus removal, CRP will begin to decline at a slower rate after peaking at 48 h. This may explain the moderate agreement between serum CRP and FebriDx CRP since they were not always collected on the same day. There are limitations to the generalizability of our study that should be noted. Firstly, the study included a selected population with an exceptionally high COVID-19 prevalence. Although in low-prevalence setting, the MxA’s NPV is expected to increase, further analysis in low prevalence setting are needed. Secondly, our study cohort included adult hospitalized patients and therefore study results study cannot be extrapolated to children nor to community dwelling patients, including those who are infected but asymptomatic or pauci-symptomatic, as it is uncertain whether their antiviral host response would be comparable to hospitalized patients. Although agreement between two investigators was necessary, we could not rule out information bias as the investigators were not blinded to the PCR SARS-CoV-2 result. To the best of our knowledge this is the first study on FebriDx performance conducted in Italy including data on immunosuppressed patients and CT counts. In summary, FebriDx MxA had high diagnostic accuracy for the identification of COVID-19 during the second wave of the pandemic and could be considered as a real-time triage tool to properly streamline the management of symptomatic, recently febrile suspected COVID-19 patients. Future research could analyze FebriDx performance, alone or combined with other rapid tests or clinical/laboratory parameters, within decision-making algorithms in order to improve the management of COVID-19 patients.

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**Conflict of interest**

None.

**Ethical approval**

Local Ethics Committees (17524/CAM_BIO) approved the study and the data collection.

**Authors contribution**

AB, FL conceived of and designed the study, oversaw the conduct of the study, conducted the analysis and wrote the
manuscript. MP, LG, GB, JM, BB, LM, MV, VS, AF, GB, CT, AB, NA, GP, VT, AM, screened, recruited patients and performed the test. ST entered the data. All authors reviewed and contributed to the manuscript revision.

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