

Utility of FebriDx in early identification of possible COVID¹⁹ infection

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Abstract

Background Reliable differentiation between uncomplicated and self-limiting acute respiratory tract infections (ARIs) and more severe bacterial respiratory tract infections remains challenging, due to the non-specific clinical manifestations in both systemic bacterial or viral infections. The current COVID-19 pandemic is putting extraordinary strain on healthcare resources. To date, molecular testing is available but has a long turnaround time and therefore cannot provide results at the point-of-care, leading to a delay in results thereby exposing patients to cross-infection and delay in diagnosis (1-3).

Methods We prospectively evaluated the utility of FebriDx®, a point-of-care fingerstick blood test that can differentiate viral from bacterial ARIs through simultaneous detection of both Myxovirus-resistance protein A (MxA) and C-reactive protein (CRP), in rapidly determining viral cases requiring immediate isolation and confirmatory molecular testing, from non-infectious patients or bacterial infections that require antibacterial therapy.

Results 75 consecutive patients were assessed and 48 eligible cases were tested with FebriDx®. Overall, 35 patients had FebriDx® test viral positive. All 35 patients had either positive rt-PCR (n=30) for COVID-19 or clinical picture highly suggestive of COVID-19 infection (PPV of 100% in a pandemic situation)[AB1]. In the 13 cases it was viral negative, rRT-PCR was also negative in all cases. In one case of LRTI, it was not possible to determine the exact cause of infection and a viral infection couldn't be excluded. Including this patient, the NPV was 12/13 (92%) exceeding the NPV of rRt-PCR at 71% (12/17). Sensitivity was conservatively calculated at 97% (35/36) compared to 85.7% (30[RS2]/35) for rRt-PCR. Similarly the specificity of both FebriDx® and rRt-PCR was 100% (12/12).

Conclusions In the current COVID-19, FebriDx® shows potential as a reliable POC test and a proxy marker of COVID-19 infection amongst inpatients in a secondary care setting.

[AB1] 35/35 equates to a sensitivity and specificity of 100% for COVID, would you be willing to say that instead of 'near 100% ppv)?

[RS2] I believe PCR was 85.7% (30/35), because PCR only detects the COVID cases

Background

Acute respiratory infection (ARI) is the most common reason patients seek healthcare worldwide. Uncomplicated ARIs in the outpatient setting are often of viral origin [acute bronchitis (90%), pharyngitis (85%), and sinusitis (98%)] or are self-limiting and tend to resolve without antibiotics.¹ Reliable differentiation between uncomplicated and self-limiting ARIs and more severe bacterial respiratory tract infections remains challenging, primarily due to the non-specific overlapping clinical manifestations

which can be present in both clinical scenarios, and secondly because many patients have hypersensitivity to, are carriers of, or are colonized with bacterial or viral pathogens.

The current COVID-19 pandemic is putting an extraordinary strain on healthcare resources. To date, only molecular testing is available (rRT-PCR), but has a long turnaround time and marginal sensitivity, and therefore cannot provide results at the point-of-care in suspected cases, leading to a delay in results and exposing patients to cross-infection and delay in diagnosis.^{2,3} FebriDx is a 10- minute, point-of-care (POC) test that uses a fingerstick blood sample to differentiate viral from bacterial ARI through simultaneous detection of both Myxovirus resistance protein A (MxA) and C- reactive protein (CRP). MxA is an intracellular protein that becomes elevated in the presence of acute viral infection and CRP is an acute-phase inflammatory protein that is elevated in the presence of a systemic bacterial and/or viral infection. FebriDx may be used to triage patients with non-specific ARI symptoms in a General Practice, Hospital or ED setting, streamlining patients for confirmatory testing and facilitating hospitalisation or discharge.^{4,5} We hypothesised that FebriDx could significantly decrease time to presumed diagnosis and allow for appropriate isolation from the outset, in suspected COVID-19 cases presenting to Hospital / ED. The primary objective was to determine positive predictive value (PPV) of FebriDx measured against the SARS-CoV-2 rRT-PCR on throat and nasal swabs and the clinical criteria. In addition, the sensitivity and specificity of FebriDx compared with rRT-PCR was calculated.

Methods

Study Design and Patients

We prospectively evaluated the use of FebriDx in 48 consecutive symptomatic ARI patients presenting in the Hospital / ED setting with suspected COVID-19 infection, in order to determine if it could rapidly identify and guide stratification between those requiring immediate isolation and confirmatory molecular testing, from non-infectious patients or bacterial infections that require antibacterial therapy alone. Inclusion and exclusion criterion are summarized in Figure 1.

FebriDx (Lumos Diagnostics, Sarasota, FL, USA) is a point-of-care (POC) lateral flow test that rapidly assesses the body's host immune response to an ARI and differentiates viral from bacterial infections. FebriDx identifies host immune response to infection and differentiates viral and bacterial ARI through the simultaneous detection of both Myxovirus resistance protein A (MxA) and C- reactive protein (CRP) directly from a fingerstick blood sample. MxA is specifically induced by the production of Type I interferon (IFN) α/β . The IFN system is a key component of the innate host response to viral infections and has immune modulating and antiviral functions.⁶ Type I IFNs are produced by many different cell types, specifically monocytes and macrophages, in response to a wide range viral infections and are found to be elevated in the presence of most acute viral infections^{5,7,8} C-reactive protein (CRP) is a nonspecific, acute-phase protein that is upregulated due to acute inflammation, including response to infection. CRP is predominately produced by the liver in response to inflammatory cytokines such as IL-6 and assists in

pathogen recognition and phagocytosis by macrophages and bacterial infection is a potent stimulus of CRP.⁹⁻¹⁷

When viral pathogens induce a clinically significant host immune response, MxA, a biomarker of the body's innate response to a viral infection, will elevate. While a bacterial infection is associated with an elevated CRP in the absence of MxA. Consistent with previous studies, an elevation of MxA with or without elevation in CRP was interpreted as a viral infection; and an elevation in CRP without MxA was interpreted as a bacterial infection. FebriDx was used according to the manufacturer package insert and results were verified by two physicians.

Patients meeting the inclusion criteria were offered the POC FebriDx test at the same time as the nasal and pharyngeal swab for viral PCR testing (COVID-19, Influenza A, Influenza B and Respiratory Syncytial Virus (RSV)). They also had standard routine blood tests and procalcitonin (PCT) measured at the same time. Patients who had recent onset of symptoms and clinical course consistent with COVID-19 infection along with bilateral infiltrates / pneumonia on CXR and lymphocytopenia were categorised as very highly suspicious of COVID-19 infection. This was confirmed by two independent physicians. Others were categorised as having a low likelihood of COVID-19 infection. Any patients with both FebriDx positive and COVID-19 (rRT-PCR) negative tests, were considered clinically to have COVID-19 infection, if the clinical suspicion of COVID-19 was high (as above).

Primary endpoint

The primary endpoint of our study was the positive predictive value (PPV) of FebriDx in identifying the patients who test positive on viral swab tests or had very high clinical likelihood of COVID-19 infection. Test results were logged and tallied against the viral swab results, as well as the clinical likelihood of COVID-19 infection.

Secondary endpoint

The secondary endpoint was the negative predictive value (NPV) of FebriDx in excluding COVID-19 infection, in hospitalised patients with respiratory tract symptoms during a pandemic situation.

Statistical Analysis

The data was summarized using descriptive statistics and results are reported as medians and interquartile ranges or means and standard deviations, as appropriate. Categorical variables are summarized numerically and percentages.

Results

The study was conducted between 26th March and 7th April 2020. 75 consecutive patients were assessed, 26 patients excluded, 25 were due to history of symptoms being longer than 7 days in duration and 1 was immunosuppressed. 49 patients were tested with FebriDx, 48 tests were completed and 1 could not be

done due to inability to obtain enough blood. Of the 48 patients enrolled, 66.7% (32/48) males and 33.3% (16/48) female and 54.2% were older than 65 years with a median age of 67 years. Patients reported symptoms for 2-7 days with a mean, median of 3.8 days and 3-day symptom onset, respectively. Fever was present at the time of testing in 85.4% (41/48) patients. Of the 48 subjects enrolled, 8.3% (4/48) had a final diagnosis categorized as non-infections, 16.7% (8/48) bacterial infection, 2.1% (1/48) as non-COVID viral infection and 72.9% (35/48) had confirmed COVID infection. Of the confirmed COVID infections, 68.6% (24/35) of the patients presented with a clinical picture highly suggestive of COVID-19 infection. FebriDx test results were positive for a viral infection in 72.9% (35/48) of cases, all of which were confirmed COVID infection, bacterial infection in 22.9% (11/48) of case and non-infectious in 4.2% (2/48) of cases. Final disposition amongst the cohort was 31.3% (15/48) of patients were sent home, 66.7% (32/48) were still admitted to the hospital and 1 patient died. Cohort characteristics are described in Table 1.

Overall, 35 patients had FebriDx test positive, and all of them had either positive rRT-PCR for COVID-19 (n=30) or a clinical picture highly suggestive of COVID-19 infection (n=5), which gives a PPV of 100% in this pandemic situation. In all 13 patients (out of the 48 tested) where FebriDx was negative for a viral infection, but positive for either a bacterial lower respiratory tract infection (LRTI) or bacterial pneumonia, rRT-PCR for COVID-19 was also negative. In one case of lower respiratory tract infection (LRTI), it was not possible to determine the exact cause of infection and a viral infection couldn't be excluded despite negative viral tests (FebriDx test, rRT-PCR for COVID-19, influenza and RSV were negative). Including this patient, the NPV of FebriDx for COVID-19 was 92%, exceeding the NPV of rRT-PCR (72.2%).

In this study, the overall sensitivity of FebriDx for COVID-19 infections was 100% (97.2% for viral infection), compared to 85.7% for the rRT-PCR. The specificity of both FebriDx and rRt-PCR was 100%. Overall diagnostic performance is summarised in Table 2.

Discussion

To our knowledge, this is the first prospective study during the SARS-CoV-2 pandemic, evaluating the utility of FebriDx in rapidly identifying, isolating and cohorting suspected cases of COVID-19 disease in a hospital / ED setting. In this study, 7 patients who in the end did not have COVID-19, were inadvertently exposed to COVID-positive patients whilst being cohorting with other suspected cases while awaiting swab rRT-PCR results (>48hours). Utilising FebriDx for enabling cohorting decisions would have avoided exposure in these cases. Similarly, 12 other patients without COVID-19 were exposed to positive study patients as a result of the similar cohorting arrangements.

Based on our robust study results, we propose that in the current SARS-CoV-2 pandemic situation, any suspected COVID-19 case with FebriDx test 'viral positive' (+MxA), should be treated as 'positive COVID-19' and cohorting with other COVID-19 positive patients. This would help avoid unnecessary exposure to

other suspected patients who may turn out to be negative on confirmatory rRT-PCR testing. If FebriDx is 'viral negative', alternative diagnoses should be considered at the outset.

In our study, FebriDx correctly identified 8/8 bacterial infections as bacterial with a sensitivity of 100%. FebriDx had 3 false positives for bacterial infection in two non-infectious patients and one clinically indeterminate patient suggesting a specificity for bacterial infection of 92.7% (37/40). Avoiding mixing these patients with other suspected COVID-19 patients whilst awaiting the results of rRT-PCR, would avoid unnecessary exposure to COVID-19 positive patients.

Our study is not without limitations. Based on the urgent need for to improve testing turnaround times and isolation strategies at our hospital, it was not possible to design and perform a multi- centre trial. Also, due to the need address the immediate needs to significantly more patients in the hospital, it was not feasible to increase study duration and thus cohort size. Many other hospitals in the area, and globally, are faced with similar delays in rRT-PCR test results and marginal sensitivity and therefore may also find benefit in incorporating a rapid POC testing strategy to improve isolation practices. Finally, patients presenting in our hospital with COVID symptoms were generally adults. Therefore, additional studies would be required to assess this strategy in children.

At the moment, in our clinical setting, and according to overwhelming data reports by the PHE , the centres for disease control and prevention of America and Europe (CDC and ECDC), the predominant virus causing hospitalisation amongst adults at present, seems to be SARS-CoV-2.¹⁹ Based on our study findings, it is evident that FebriDx can be successfully deployed as a reliable triage test amongst inpatients in this pandemic situation.

Declarations

Lumos Diagnostics kindly supplied the testing kits and had no role in the conduct of the study.

No other funding was required.

The authors declare no competing interests.

This study was approved by Organisational Research committee of Kettering General Hospital (NHS) Foundation Trust. As this project was a Post Market Surveillance (PMS) study of a CE marked device, the research committee confirms that no HRA or REC approval was required. Consent was obtained from all patients who participated in study by the investigators.

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Table

Due to technical limitations the Tables are available as a download in the Supplementary Files.

Figures

<p><i>Inclusion criteria</i></p> <ol style="list-style-type: none"> 1. Age >16 years 2. Patients requiring admission for at least one night with suspected COVID-19 infection (see case definition) 3. Inpatients who meet the Public Health England (PHE) criteria for swab testing for COVID-19 infection (inpatients with new respiratory symptoms or fever without another cause or worsening of a pre-existing respiratory condition)
<p><i>Exclusion criteria</i></p> <ol style="list-style-type: none"> 1. Patients who don't consent for pinprick testing 2. Patients who don't meet the PHE criteria for swab testing for COVID-19. 3. Live vaccination or antiviral treatment in the last 14 days 4. Symptoms of more than 7 days duration 5. Patient on any immunosuppressive therapy or systemic corticosteroids

Figure 1

Inclusion / Exclusion Criterion

Public Health England (PHE) Case definition of COVID-19 infection:

- Have either clinical or radiological evidence of pneumonia or
- Acute respiratory distress syndrome or
- Influenza like illness (fever $\geq 37.8^{\circ}\text{C}$ and at least one of the following respiratory symptoms, which must be of acute onset: persistent cough (with or without sputum), hoarseness, nasal discharge or congestion, shortness of breath, sore throat, wheezing, sneezing

Figure 2

COVID Case Definition

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Tables.pdf](#)
- [SummarySlide.pdf](#)