Utility of the FebriDx point-of-care test for rapid triage and identification of possible coronavirus disease 2019 (COVID-19)

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Abstract

Abstract Background Differentiating viral from bacterial acute respiratory infections (ARIs) remains challenging, due to the non-specific clinical manifestations. The 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 (POC) thereby exposing COVID-19/Non-COVID-19 patients to each other while awaiting diagnosis. Methods This observational study prospectively evaluated the utility of a triage strategy including FebriDx, a POC fingerstick blood test that differentiates viral from bacterial ARIs through simultaneous detection of 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 requiring antibiotics. Results 75 consecutive patients were screened, 48 eligible cases were tested with FebriDx, 36 were confirmed viral infection and 35/36 had COVID-19. 31/35 COVID-19 cases tested positive for SARS-CoV-2 via rRT-PCR and (4/35) had a clinical diagnosis of probable COVID-19 based on symptoms, epidemiological history, and chest imaging (PPV 100% (35/35)). 13 cases were FebriDx viral negative and rRT-PCR was also negative. In one case, it was not possible to determine the exact cause of infection, although a viral infection could not be excluded. Including this patient, FebriDx NPV was 92.3% (12/13), exceeding the NPV of rRT-PCR a 68.3% (13/19), and diagnostic sensitivity was conservatively calculated at 97% (35/36) compared to 82.9% (29/35) for initial rRT-PCR. The diagnostic specificity of both FebriDx and rRT-PCR was 100%. Conclusions: FebriDx could be deployed as part of a reliable triage strategy for identifying possible COVID-19 patients with symptomatic ARI in the COVID-19 pandemic. Key words: Pandemic; COVID-19; SARS-CoV-2; pneumonia; viral; point of care; infection

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What's known?

- COVID-19 rRT-PCR long turnaround time and marginal sensitivity have led to delays in test results, diagnosis and thus have exposed non-COVID-19 patients to cross-infection.
- FebriDx, a rapid, point-of-care diagnostic test, that identifies bacterial, viral infection (or no infection) and may be able to improve time to diagnosis and cohorting practices.

What's new?

- FebriDx was found to be highly sensitive and specific for identifying COVID-19 infections.
- FebriDx identified all patients with bacterial infection which could reduce exposure to patients with suspected COVID-19 whilst awaiting rRT-PCR results.
- FebriDx testing (minutes) can improve time to initial triage and isolation when compared to rRT-PCR (hours).

Abstract

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Results 75 consecutive patients were screened, 48 eligible cases were tested with FebriDx, 36 were confirmed viral infection and 35/36 had COVID-19. 31/35 COVID-19 cases tested positive for SARS-CoV-2 via rRT-PCR and (4/35) had a clinical diagnosis of probable COVID-19 based on symptoms, epidemiological history, and chest imaging (PPV 100% (35/35)). 13 cases were FebriDx viral negative and rRT-PCR was also negative. In one case, it was not possible to determine the exact cause of infection, although a viral infection could not be excluded. Including this patient, FebriDx NPV was 92.3% (12/13), exceeding the NPV of rRT-PCR a 68.3% (13/19), and diagnostic sensitivity was conservatively calculated at 97% (35/36) compared to 82.9% (29/35) for initial rRT-PCR. The diagnostic specificity of both FebriDx and rRT-PCR was 100%.

Conclusions : FebriDx could be deployed as part of a reliable triage strategy for identifying possible COVID-19 patients with symptomatic ARI in the COVID-19 pandemic.

Key words: Pandemic; COVID-19; SARS-CoV-2; pneumonia; viral; point of care; infection

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 viral from bacterial ARIs remains challenging, primarily due to the non-specific overlapping clinical manifestations which can be present in both clinical scenarios, and secondly because many patients are carriers of or are colonized with bacterial or viral pathogens.

The COVID-19 pandemic is putting an extraordinary strain on healthcare resources. To date, molecular reverse transcriptase polymerase chain reaction (rRT-PCR) has been used for screening and initial diagnosis

despite long turnaround times that can take upwards of 48 hours from sample collection to result. Some patients, including those with high likelihood COVID-19 infection (e.g. symptomatic with recent exposure and chest imaging consistent with COVID-19 infection), test negative on the initial RT-PCR test which requires multiple subsequent tests to return an eventual positive result.[2-4] Variations of sampling techniques, viral load and analytical sensitivity of the manufacturer test kit may impact sensitivity.[5] Molecular tests are also impacted by efficiency of viral sample transfer to the test and can differ depending on sampling technique (oropharyngeal vs. nasopharyngeal).[6,7] This may offer an explanation as to why early data from China reported test sensitivities ranging from 66-70%.[5,8] Recently, studies comparing rRT-PCR to a composite of radiological plus clinical findings (signs/symptoms, epidemiological evidence of exposure) have reported that that chest imaging improves initial diagnosis of COVID-19 and is associated with fewer false negatives.[2,9] Therefore, a comprehensive clinical diagnosis inclusive of clinical exam (symptoms/signs), laboratory findings, confirmatory testing (i.e. RT-PCR), and chest imaging may also be considered as indictors of COVID-19 to reduce false negative rate of molecular testing.[9-12]

Rapid host response assays have been proposed for initial triage as components of a comprehensive COVID-19 diagnostic strategy that also includes molecular and antibody testing. This is in an effort to streamline patients for confirmatory testing, quarantine and facilitate hospitalisation or discharge.[13] FebriDx, (Lumos Diagnostics, Sarasota, FL, USA) is a point-of-care (POC) immunoassay that rapidly (10 minutes) assesses a host immune response to an ARI and differentiates viral from bacterial infection through detection of both Myxovirus resistance protein A (MxA) and C-reactive protein (CRP) from a fingerstick blood sample.

CRP is a nonspecific, acute-phase protein that is upregulated due to acute inflammation, including response to infection and is predominately produced by the liver in response to inflammatory cytokines such as IL-6. [14-22] MxA is an intracellular protein that is exclusively induced by type I IFN and not by other cytokines expressed during bacterial infection (e.g. IFN-gamma, IL-1, TNF-alpha.[23] Type I IFNs are produced by many different cell types, specifically monocytes and macrophages, in response to a wide range of viral infections and are found to be elevated in the presence of most acute viral infections.[24-26] Therefore, MxA is elevated in response to an acute viral infection and remains low in bacterial infections.[24,25] It is hypothesised that SARS-CoV-2 may initially suppress type I IFN production causing loss of viral containment early in of infection followed by an influx of neutrophils, macrophages and excessive production of type I IFN.[27]However, considering that MxA is exclusively expressed by type 1 IFNs and similar viruses such as MERS-CoV and SARS-CoV have been found to elevate MxA, it is likely that MxA would also increase in response to SARS-CoV-2 infection.[28]

FebriDx, utilizes monoclonal anti-MxA and anti-CRP antibodies to detect elevated levels of MxA and CRP respectively. MxA elevation with or without an elevation in CRP is consistent with a viral infection. An elevation in CRP without MxA is consistent with a bacterial infection that may require antibiotic therapy. Two multicentre trials demonstrated that FebriDx was sensitive and specific to differentiate viral from bacterial and non-infectious conditions in patients presenting to General Practice offices as well as Hospital or Emergency Department (ED) settings, with non-specific ARI symptoms.[24,25]

Therefore, we hypothesised that FebriDx would provide an early indication of a host immune response in suspected COVID-19 cases presenting to Hospital / ED. Identifying patients as having a bacterial or viral infection or non-infectious condition could significantly decrease time to presumed diagnosis and allow for appropriate isolation from the outset. The primary objective was to assess the FebriDx assay ability to identify COVID-19 patients as viral infections in order to inform clinical management strategies and initial isolation procedures until confirmatory testing results are available. As such, diagnostic performance of FebriDx was measured against the Case Definitions for Bacterial Infection, COVID-19 Viral Infection[29], Non-COVID-19 Viral Infection and Non-Infectious conditions and were confirmed by an independent physician (Figure 1). In addition, the diagnostic performance of SARS-CoV-2 rRT-PCR was also compared to the COVID-19 Case Definition.[30,31]

Methods

Study Design and Patients

Patients presenting in the Hospital or ED of Kettering General Hospital, a 600-bed acute care hospital in Kettering, England, with suspected COVID-19 infection were prospectively screened for eligibility. Patients were considered to be eligible if they were 16 years or older, met the Public Health England (PHE) criteria for swab testing for COVID-19 including the requirement of hospital admission and having either clinical or radiological evidence of pneumonia or acute respiratory distress syndrome or influenza like illness (fever [?]37.8°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), or inpatients with new respiratory symptoms or fever without another cause or worsening of a pre-existing respiratory condition.[32] Patients were not eligible if they did not consent to participate, did not meet PHE criteria for COVID-19 swab testing, received a live vaccine or antivirals in the last 14 days, had respiratory symptoms for more than 7 days, or were taking immunosuppressive therapy or systemic corticosteroids. Consent was obtained from patients prior to inclusion in the study. The POC FebriDx test was offered at the same time as the nasal and pharyngeal swab for viral PCR testing (SARS-CoV-2, Influenza A, Influenza B and Respiratory Syncytial Virus (RSV)). Standard routine blood tests (e.g. Complete blood cell count (CBC), CRP, and procalcitonin (PCT)) were also performed. SARS-CoV-2 rRT-PCR testing was repeated, based on availability as tests were very limited early in the COVID-19 pandemic, if there was strong clinical suspicion of COVID-19 infection and an initial test was negative. Final disposition data was collected four weeks after enrollment. Eligibility and workflow are summarized in Figure 1.

Reference Method Case Definitions

Patients were categorized as having a final diagnosis of Bacterial Infection[33,34], COVID-19 Viral Infection[30,31], Non-COVID-19 Viral Infection[33,34] and Non-Infectious conditions[33,34] were based on the following Case Definitions (Figure 1). The Case Definition for COVID-19 Viral Infection was a composite of (i) clinical findings (e.g. fever [?]37.8degC 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), inpatients with new respiratory symptoms or fever without another cause or worsening of a pre-existing respiratory condition cough, shortness of breath, or difficulty breathing and; (ii) epidemiological evidence of recent exposure to COVID-19 and; (iii) either positive SARS-CoV-2 rRT-PCR or a combination of radiological changes consistent with COVID 19 along with lymphocytopenia and lack of an alternative diagnosis. Due to a lack of a gold standard for COVID-19 diagnosis, the Case Definition for COVID-19 Viral infection was informed by guidance from both the European Centre for Disease Prevention and Control (ECDC) and the U.S. Centers for Disease Control and Prevention (CDC).[30,31] Patients were considered to have a final diagnosis (i.e. Case Definition) of Bacterial LRTI/Pneumonia if found to have negative molecular viral testing (SARS-CoV-2, RSV, Influenza) and one of the following: 1) chest imaging with new onset focal consolidation and CRP [?]100 mg/L[34] and PCT [?]0.25ng/mL[33] (bacterial pneumonia)] or 2) No consolidation on chest imaging and CRP [?]40[34] mg/L and PCT [?]0.1ng/mL[33] (bacterial LRTI) with or without positive bacterial culture. The Case Definition for a Non-COVID-19 Viral Infection was defined as the absence of bacterial pathogen or positive rRT-PCR detection of a non-COVID-19 viral respiratory pathogen and laboratory findings consistent with viral infection such as lymphocytosis, PCT <0.1ng/mL[33], CRP <40 mg/L[34]; The Case Definition for a Non-Infectious condition was defined as having clear evidence of alternative diagnosis with absence of a detected pathogen, chest imaging that was negative for consolidation/infiltrates consistent with infection, Procalcitonin <0.1 ng/mL.[33] The final diagnosis, based on the Case Definitions described above, was confirmed by an independent physician.

FebriDx Interpretation

FebriDx was used according to the manufacturer package insert and a second physician was consulted to verify the results of all viral negative tests as well as those where the physician performing the test requested help interpreting the colour saturation of the FebriDx test lines. Consistent with previous studies[24,25], 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. The absence of an elevation in either CRP or MxA was interpreted as negative.

Primary Endpoint

The diagnostic performance (Sensitivity, Specificity, Positive Predictive Value (PPV), Negative Predictive Value (NPV)) of FebriDx to determine if COVID-19 patients, as defined by the Case Definition for COVID-19[30,31] (Figure 1), would be identified as a viral infection in hospitalised patients with ARI symptoms (Figure 3).

Secondary Endpoint

The diagnostic performance of SARS-CoV-2 rRT-PCR testing was compared to the Case Definition for COVID-19[30,31] (Figure 3).

Statistical Analysis

Sample size was not prespecified. 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. Diagnostic Sensitivity, Specificity, PPV, NPV are reported as point estimates and 95% confidence intervals.

Results

The study was conducted at Kettering General Hospital, Kettering England, between the 26th of March and 7th of April 2020. A total of 75 consecutive patients were screened for eligibility and 26 patients were deemed ineligible due to history of symptoms being longer than 7 days in duration (n=25) and immunosuppression (n=1). FebriDx testing was performed on 49 patients, test results were obtained for 48/49 patients and testing was not possible in 1/49 patients due to an inability to obtain enough blood on the first attempt. A second attempt was not possible as the patient was elderly, frail and clinically unstable at the time of testing. Data from 48 patient were included for final analysis (Figure 2). Of the 48 patients enrolled, 66.7% (32/48) males and 33.3% (16/68) female and 54.2% (26/48) were older than 65 years with a median age of 67 years. Enrolled 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) of patients. The final disposition amongst the cohort was 75% (36/48) of patients were discharged home, 25% (12/48) died while hospitalised. Cohort characteristics are described in Table 1.

Of the 48 subjects enrolled, 8.3% (4/48) had a final diagnosis categorised as non-infectious, 16.7% (8/48) bacterial infection, 2.1% (1/48) as non-COVID-19 viral infection and 72.9% (35/48) COVID-19 infection based on the Case Definitions[30,31] (Figure 3). The overall prevalence of COVID-19 infection in the cohort was 72.9% (35/48) and the FebriDx test results were positive for a viral infection in all cases that had a final diagnosis of COVID-19 Viral infection. FebriDx was positive for bacterial infection in 22.9% (11/48) of cases and 100% (8/8) had a final diagnosis of Bacterial Infection (Sensitivity 100% [95% CI 63.1-100.0], Specificity 92.5% [95% CI 79.6-98.4], NPV 100% [95% CI 90.5-100.0], PPV 72.7% [95% CI 39.0-94.0] (Table 2). In all cases where FebriDx was negative for a viral infection (13/48), SARS-CoV-2 rRT-PCR 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 could not be excluded despite negative viral tests (FebriDx test, rRT-PCR for SARS-CoV-2, influenza and RSV were negative). Therefore, this patient was classified as having a final diagnosis of Non-COVID-19 Viral. Including this patient, in primary endpoint analysis, FebriDx demonstrated a diagnostic sensitivity 97.2% [95% CI 85.5 - 99.9], specificity of 100% [95% CI 73.5 - 100.0], PPV of 100% [95% CI 90.0 - 100.0], and NPV of 92.3% [95% CI 64.0 - 99.8] for viral infection (COVID-19 and Non-COVID-19) (Table 2).

In secondary endpoint analysis, SARS-CoV-2 was detected by rRT-PCR in (31/35) cases with a final diagnosis of COVID-19 Viral infection; 82.9% (29/35) were detected on the first rRT-PCR test (test to confirmation, 48 hours), 5.7% (2/35) were detected on the second rRT-PCR test (test to confirmation, 96 hours), and 11.5%

(4/35) SARS-CoV-2 were not detected by rRT-PCR despite clear clinical evidence of COVID-19 that was consistent with Case Definition[30,31]. Of the 4 patients that met the Case Definition for COVID-19, but where SARS-CoV-2 was not detected using rRT-PCR, one had a positive SARS-CoV-2 IgM/IgG antibody test 14 days after the initial negative rRT-PCR test. FebriDx was viral positive in this patient.

FebriDx demonstrated a diagnostic sensitivity of 100% [95% CI 90.0-100], specificity of 100% [95% CI 75.3-100.0], PPV of 100% [95% CI 90.0-100], and NPV of 100% [95% CI 75.3-100.0] for identifying COVID-19 infection in a setting in which most ARIs were expected to be caused by SARS-CoV-2 (i.e. a high prevalence of SARS-CoV-2 infection was expected). Initial rRT-PCR (i.e. the very first rRT-PCR result obtained from patients) demonstrated a diagnostic sensitivity of 82.9% [95% CI 66.4-93.4], specificity of 100% [95% CI 75.3-100], PPV of 100% [95% CI 88.1-100], and NPV of 68.4% [43.4-87.4] when compared to the COVID-19 Case Definition[30,31] (Table 2).

Discussion

Our study prospectively evaluated the utility of FebriDx to rapidly identify suspected cases of COVID-19 disease in a hospital / ED setting in an effort to improve isolation and cohorting procedures. Forty-nine patients were enrolled, and one patient was excluded after enrollment due to the inability to obtain enough blood for FebriDx testing after the first attempt. Due to the patient's advanced age and unstable clinical state at the time of testing, FebriDx testing was not repeated and thus this patient was excluded from the analyses. Therefore, 48 patients were included in the analyses of the for the primary and secondary endpoints. After using PHE screening criteria for suspected COVID-19 signs/symptoms, FebriDx correctly identified all patients (35/35) who met the Case Definition[30,31] for COVID-19 (Figure 3). FebriDx also correctly identified all patients that had a bacterial infection by case definition (8/8) which resulted in a diagnostic sensitivity of 100%. FebriDx had three false positives for bacterial infection in two non-infectious patients and one clinically indeterminate patient demonstrating a specificity for bacterial infection of 92.5% (37/40) (Table 2). **T** he mortality rate for COVID-19 related deaths was 33.3% our cohort. This is in keeping with COVID-19 related mortality rates for hospitalised patients within our health system as well as the national mortality figures for hospitalised patients.[35] Standalone conventional CRP was elevated in both COVID-19 viral cases and bacterial cases in our study (median [IQR] 76 mg/L [50.3-115.5]; 94 mg/L [59.5.0-152.0], respectively). Brendish et al., also found CRP to be elevated in both COVID and Non-COVID-19 cases (median (range) 83 mg/L (32-136 mg/L); 33 (9-114 mg/L) respectively $p<0.0001$).[36]Although Brendish et al. found the difference to be statistically significant, the considerable overlap of quantitative CRP may make it difficult to differentiate viral from bacterial infection as a standalone test.[36] The same appears to apply to procalcitonin and leukocyte count in our study (Table 1). MxA confers the diagnostic sensitivity and specificity needed to differentiate elevated CRP associated with viral vs. bacterial infection and may help to avoid mixing non-COVID-19 with COVID-19 whilst awaiting the results of rRT-PCR that can take up to 48 hours in the hospital/ED settings. In our study 7 patients, who in the end were not diagnosed with COVID-19, were inadvertently exposed to COVID-19 due to the unintended mixed cohorting that occurred whilst awaiting swab rRT-PCR results. As our study was intended to evaluate diagnostic accuracy of FebriDx as part of an initial triage strategy, the FebriDx test results were not used to make decisions regarding cohorting until after the study was concluded and the results were analysed. Based on the high NPV of FebriDx in our setting, it is possible that the unintended exposure of non-COVID-19 patients could have been avoided if FebriDx was utilised part of the initial triage of ARI patients with suspected COVID-19. Utilising FebriDx for enabling cohorting decisions could have avoided exposure in these cases.

A recent study by Brendish and colleagues from University Hospital Southampton, Southampton, England, also evaluated the diagnostic accuracy of FebriDx in 248 hospitalised adults who presented with suspected COVID-19 regardless of duration of symptom onset (inclusive of the PHE Case Definition for Possible Infection).[36,37]Of the 248 patients who underwent FebriDx and SARS-CoV-2 rRT-PCR, 118 had SARS-CoV-2 detected (prevalence 48%). Diagnostic sensitivity, specificity, NPV and PPV were 93%, 86%, 86% and 93%, respectively. Despite some methodological differences their results were comparable to our study.

Based on the diagnostic performance characteristics of FebriDx demonstrated in our study as well as Brendish

et al.[36], we propose that in the current SARS-CoV-2 pandemic situation, patients presenting with signs and symptoms of ARI and suspected of COVID-19 infection should be tested with FebriDx test as part of the initial diagnostic triage process. Those testing 'viral positive' (+MxA), should be treated as 'positive COVID-19' and cohorted 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 result is 'viral negative' an alternative diagnosis such as bacterial infection or non-infectious conditions such as bacterial pneumonia or LRTI, should be considered at the outset. It should be noted however, that patient enrollment took place at the peak of the COVID-19 outbreak in our region and pre-test probability of recruiting COVID-19 positive patients was relatively high. This strategy allowed us to obtain a maximum number of potential COVID-19 infections to evaluate FebriDx-based identification of SARS-CoV-2 infection. Therefore, the prevalence of COVID-19 infection was 73.2% in our setting and this may have increased the chance of obtaining a high PPV.

Future viral outbreaks and seasonal infections could be managed, ideally, by optimizing all available diagnostic tools (e.g. clinical assessment, host response, molecular testing, antibody testing etc.).[13] Pulia et al. proposed 'Multi-tiered Screening and Diagnostic Strategy' that incorporates a comprehensive approach that could be used in the SARS-CoV-2 pandemic and potentially as a general strategy in future pandemics.[13] The strategy proposes that after initial screening (e.g. clinical signs/symptoms of the suspected infection), such as the initial screening performed in our study, patients could be (i) be quickly tested for a viral, bacterial or absent immune response to an infection, followed by (ii) rapid confirmatory pathogen-specific testing; and (iii) rapid antibody testing could be performed in patients that present with greater than 7 days of symptom onset to confirm a recent or past infection. Although FebriDx should not be used as a surrogate for pathogen-detection tests, it can be applied to rapidly categorise patients as having bacterial or viral infections or non-infectious conditions as part of the diagnostic triage process.[36] This would allow bacterial infections/non-infectious conditions to be cohorted separately from suspected viral infections. Those with viral infections would go on to have confirmatory testing to improve cohorting within the viral category, whereas antibiotics could be considered for patients positive for bacterial infection. Repeat rRT-PCR testing could be considered in high risk patients who test viral positive on FebriDx but have a negative initial SARS-CoV-2 PCR.

Our study is not without limitations. Based on the urgent need to improve testing turnaround times and patient isolation strategies at our hospital, it was not possible to design and perform a multi-centre trial that included a control group. Antibody testing was not available for all patients enrolled nor is antibody testing required by PHE, ECDC nor CDC for confirmation of COVID-19 infection. That said, antibody confirmation would be ideal for determining definitive COVID-19 infection after 14 days of symptom onset, especially in cases that have a high clinical suspicion but were SARS-CoV-2 is not detected by rRT-PCR testing. Due to the lack of a gold standard test for COVID-19 infection, the current assessment of the performance characteristics of rRT-PCR may suffer from an incorporation bias. We attempted to mitigate this by including clinical, radiological, and epidemiological criteria for final diagnosis of COVID-19 infection as is consistent with the ECDC and CDC Case Definitions. Finally, patients presenting in our hospital with COVID-19 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, CDC and ECDC, the predominant virus causing hospitalisation amongst adults at present, seems to be SARS-CoV-2.[28] Based on our study findings, we provide evidence that FebriDx could be deployed as part of the initial diagnostic triage process for early identification of symptomatic COVID-19 patients presenting in a hospital setting.

Disclosures

Authors declare that they have no conflicts of interest.

Funding

Lumos Diagnostics kindly supplied the testing kits and funding for publication fees but had no role in the conduct of the study.

Compliance with Ethics Guidelines

Prior to enrollment, the study was submitted for review to the Kettering General Hospital Ethics Committee and granted approval by the Research Committee Chair. Informed Consent was obtained from all participants and failure to consent was considered an exclusion criterion.

Data Availability

The datasets during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Table 1. Cohort Characteristics

Characteristic no. (%)	Total Cohort (n=48)	Viral (COVID-19/ Non-COVID-19) (n=36)	Bacterial (n=8)	Non-Infectious (n=4)
Sex no. (%)				
Male	32 (66.7)	26 (72.2)	4 (50.0)	2 (50.0)
Female	16 (33.3)	10 (27.8)	4 (50.0)	2 (50.0)
Age – years, no. (%)				
< 65	22 (45.8)	17 (47.2)	4 (50.0)	1 (25.0)
[?] 65	26 (54.2)	19 (52.8)	4 (50.0)	3 (75.0)
Range	24-96	24-96	28-94	50-82
Mean (SD)	64.3 (+/- 18.8)	63.8 (+/- 18.2)	62.5 (+/- 24.0)	72 (+/- 14.9)
Median [IQR]	67 [54-78]	67 [54-77]	69 [49-78]	78 [69-80]
Symptom Onset – days				
Range	2-7	2-7	2-5	2-7
Mean, (SD)	3.8, (+/-1.8)	4, (+/-1.9)	2.9, (+/-1.2)	3.8, (+/-2.2)
Median [IQR]	3 [2-5]	3 [2-5]	2 [2-3]	3 [3-4]
Fever ([?] 37.8*C) no. (%)				
Yes	41 (85.4)	34 (94.4)	6 (75.0)	1 (25.0)
No	7 (14.6)	2 (5.6)	2 (25.0)	3 (75.0)
Final Disposition no. (%)				
Home	36 (75.0)	27 (75.0)	7 (87.5)	2 (50.0)
Died	12 (25.0)	9 (25.0)	1 (12.5)	2 (50.0)
Final Diagnosis no. (%)				
COVID/Viral	35 (72.9)	35 (97.2)	0 (0)	0 (0)
Non-COVID	1 (2.1)	1 (2.8)	0 (0)	0 (0)

Characteristic no. (%)	Total Cohort (n=48)	Viral (COVID-19/ Non-COVID-19) (n=36)	Bacterial (n=8)	Non-Infectious (n=4)
Bacterial	8 (16.7)	0 (0)	8 (100)	0 (0)
Non-Infectious	4 (8.3)	0 (0)	0 (0)	4 (100)
FebriDx Results no. (%)				
Viral	35 (72.9)	35 (97.2)	0 (0)	0 (0)
Bacterial	11 (22.9)	1 (2.8)	8 (100)	2 (50.0)
Non-Infectious	2 (4.2)	0 (0)	0 (0)	2 (50.0)
Procalcitonin (ng/mL)				
Range	0.05-13.6	0.05-13.6	0.08-0.68	0.09-0.09
Median, [IQR]	0.17, [0.08-0.33]	0.2, [0.08-0.33]	0.24, [0.14-0.41]	0.09, [0.09-0.09]
C-Reactive Protein (mg/L)				
Range	5-310	5-304	32-310	5-34
Median, [IQR]	74 [38-115]	74 [49-115]	94 [60-152]	16.5 [11-23]
Leukocyte Count				
Range	2.6-19.1	2.6-13.9	10.5-19.1	9.7-15.7
Median, [IQR]	9 [5-11]	8 [4-10]	13 [11-16]	12 [10 -14]
Lymphocyte Count				
Range	0.4-8.4	0.4-8.4	0.6-6.4	1.2-6.4
Median, [IQR]	0.95 [0.7-1]	0.8 [0.7-1.2]	1.4 [0.8-1.7]	2 [1.6-3.3]

IQR, Interquartile Range; SD, Standard Deviation

Table 2. FebriDx and rRT-PCR Diagnostic Performance Characteristics following initial screening (e.g. clinical signs/symptoms of COVID-19)

	Sensitivity T
PRIMARY ENDPOINT(S) **FebriDx Viral vs. Case Definition (Viral-all)**	97.2% 35/36
FebriDx Viral vs. Case Definition (COVID-19 Viral)	100% 35/35
SECONDARY ENDPOINT **Initial SARS-CoV-2 rRT-PCR vs. Case Definition (COVID-19 Viral)**	82.9% 29/35
ADDITIONAL ENDPOINT **FebriDx Bacterial vs. Case Definition (Bacterial)**	100% 8/8 [63

TN, True Negative, TP, True Positive; FN, False Negative; FP, False Positive; PPV, positive predictive value; rRT-PCR, reverse transcriptase polymerase chain reaction; NPV, negative predictive value, NA, not applicable.

Figure 1 – Eligibility Criteria, Workflow and Case Definitions for Final Diagnosis Categorisation (atttached as a separate image)

Figure 2. Screened and Enrolled Patients (atttached as a separate image)

Figure 3. Final Diagnosis Categorisation (atttached as a separate image)

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febridx-point-of-care-test-for-rapid-triage-and-identification-of-possible-coronavirus-disease-2019-covid-19

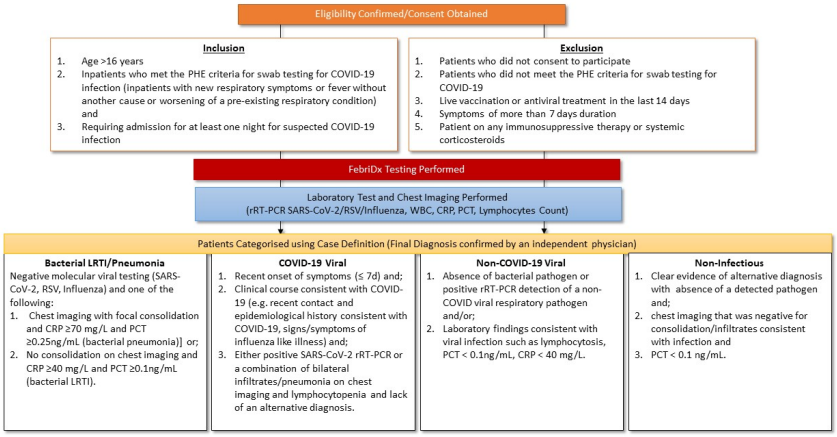

Figure 1. Eligibility Criteria, Workflow and Case Definitions for Final Diagnosis Categorisation

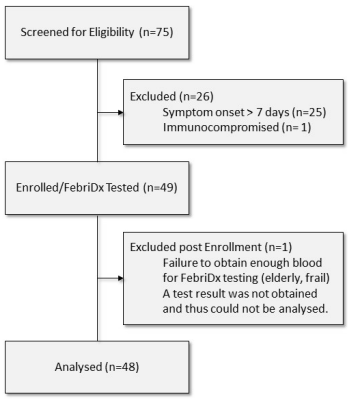

Figure 2. Study Cohort

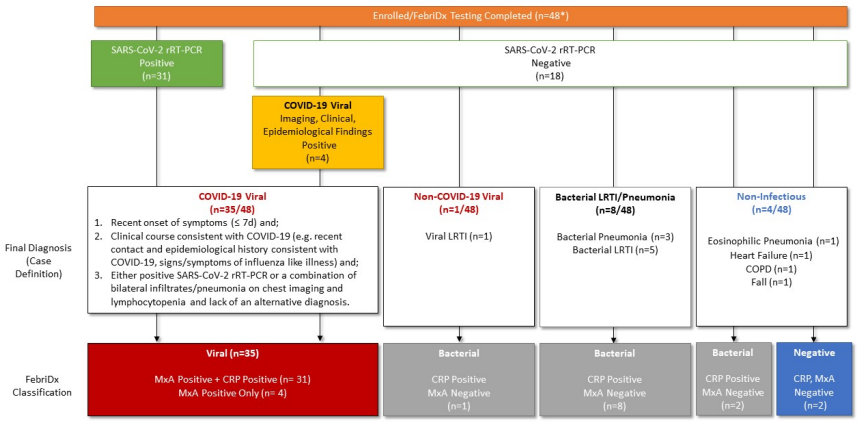

Figure 3. Case Definitions for Final Diagnosis compared to FebriDx and SARS-CoV-2 RT-PCR.
* 1 patient excluded due to failure to obtain fingerstick sample