**FebriDx host response point-of-care testing improves patient triage for COVID-19 in the emergency department**

Christopher T. Mansbridge1, Alex R. Tanner1, Kate R. Beard1,2, Florina Borca2,3,4, Hang T.T. Phan2,3,4, Nathan J. Brendish1,4, Stephen Poole1,2,4,5, Christopher Hill6, Michael Kiuber6, Robert Crouch6,7, Daniel Waddington6, and Tristan W. Clark1,2,4,5\*

1. Department of Infection, University Hospital Southampton NHS Foundation Trust, Southampton, UK.

2. NIHR Southampton Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust, Southampton, UK

3. Clinical Informatics Research Unit, University of Southampton, Southampton, UK

4. School of Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton, Southampton, UK

5. NIHR Post Doctoral Fellowship Programme, UK

6. Department of Emergency Medicine, University Hospital Southampton NHS Foundation Trust, Southampton, UK.

7. Health Sciences, Faculty of Environmental and Life Sciences, University of Southampton, Southampton, UK

\*Corresponding author

Dr Tristan William Clark, Associate Professor and Consultant in Infectious Diseases. NIHR Post Doctoral Fellow.

Address: LF101, South Academic block, Southampton General Hospital, Southampton, SO16 6YD.

Tel: 0044(0)23818410 E-mail address: T.W.Clark@soton.ac.uk

**Keywords**

FebriDx; COVID-19; Myxovirus resistance protein; emergency department; triage; accuracy

**Running title**

FebriDx use in the emergency department

**Word count**

3000

**Full author details**

Dr Christopher T. Mansbridge, MRCP, Speciality Registrar in Infectious Diseases, University Hospital Southampton NHS Foundation Trust, Hampshire, United Kingdom

Dr Alex R. Tanner, BMBS, Clinical Research Fellow in Infectious Diseases, University Hospital Southampton NHS Foundation Trust, Hampshire, United Kingdom

Dr Kate Beard, MRCP, Speciality Registrar in Infectious Diseases, University Hospital Southampton NHS Foundation Trust, Hampshire, United Kingdom

Florina Borca, MSc, Senior Information Analyst for Research & Development, University of Southampton, Hampshire, United Kingdom

Hang T.T. Phan, PhD, Data Science Technical Lead, University of Southampton, Hampshire, United Kingdom

Dr Nathan J. Brendish, PhD, NIHR Clinical Lecturer in Infectious Diseases, University of Southampton, Hampshire, United Kingdom

Dr Stephen Poole, MRCP, NIHR Biomedical Research Centre Clinical Research Fellow in Infectious Diseases, University Hospital Southampton NHS Foundation Trust, Hampshire, United Kingdom

Dr Christopher Hill, FCEM, Consultant in Emergency medicine, University Hospital Southampton NHS Foundation Trust, Hampshire, United Kingdom

Dr Michael Kiuber, FCEM, Consultant in Emergency medicine, University Hospital Southampton NHS Foundation Trust, Hampshire, United Kingdom

Professor Robert Crouch, PhD, Professor in Emergency care, University Hospital Southampton NHS Foundation Trust, Hampshire, United Kingdom

Dr Daniel Waddington, FCEM, Consultant in Emergency medicine, University Hospital Southampton NHS Foundation Trust, Hampshire, United Kingdom

Dr Tristan W. Clark, MD, Associate Professor and Honorary Consultant in Infections Diseases, University of Southampton, Hampshire, United Kingdom

**ABSTRACT**

**Objective:** Patients presenting to hospital with suspected COVID-19, based on clinical symptoms, are routinely cohorted together until PCR test results are available. This leads to delays in transfers to definitive areas and high nosocomial transmission rates. FebriDx is a finger-prick point-of-care test (POCT) that detects an antiviral host response and has high negative predictive value for COVID-19. We aimed to determine the clinical impact of using FebriDx for COVID-19 triage in the emergency department.

**Design:** We undertook a retrospective observational study evaluating the real-world clinical impact of FebriDx as part of an ED COVID-19 triage algorithm.

**Setting:** Emergency department of a university teaching hospital.

**Patients:** Patients presenting with symptoms suggestive of COVID-19, and cohorted in ‘high-risk’ areas, were tested by FebriDx. Patients without detectable antiviral host response were then moved to lower-risk areas.

**Results:** Between 22 September 2020 and 7 January 2021, 1321 patients were tested by FebriDx and 1104 (84%) did not have a detectable antiviral host response. 865/1104 (78%) patients were moved to lower-risk areas within the ED. Median time spent in high-risk areas was 52 (IQR 34 to 92) minutes for FebriDx-negative patients and 203 (IQR 142 to 255) minutes for FebriDx-positive patients (difference of -134 minutes, 95%CI -144 to -122; p<0.0001). The negative predictive value of FebriDx for the identification of COVID-19 was 96% (661/690, 95%CI 94 to 97).

**Conclusions:** FebriDx improved the triage of patients with suspected COVID-19 and reduced the time that SARS-CoV-2 PCR-negative patients spent in high-risk areas alongside positive patients.

**Introduction**

The management of the COVID-19 pandemic is hindered by long delays in diagnosis. Due to limited availability of single room accommodation in UK hospitals, patients are routinely cohorted together based on clinical symptoms, until diagnostic test results are available.[1](#_ENREF_1) This results in delays in transfers to definitive clinical areas and high rates of nosocomial transmission.[2](#_ENREF_2), [3](#_ENREF_3) Although molecular point-of-care tests (POCTs) have dramatically reduced times to diagnosis,[4](#_ENREF_4) the availability of such tests are limited and, in addition to high cost, this represents a barrier to their widespread routine use.

Emergency departments (EDs) are busy and often overcrowded places and represent a high-risk clinical area for transmission of SARS-CoV-2 between patients. The unsuitability of current UK EDs for managing patients in the context of a pandemic with a highly transmissible infectious agent has been recognised at a national level.[5](#_ENREF_5) In addition to the limited physical space in EDs, the lack of real-time diagnostic results compounds the problem and leads to poor patient flow as patients deemed at high-risk of having COVID-19 based on symptoms are nursed together in ‘high-risk’ cohort areas until they are admitted or discharged.[1](#_ENREF_1) The lack of single occupancy rooms or adequately distanced bay areas in EDs means that patients without COVID-19 in these high-risk cohort areas are at great risk of acquiring the infection from neighbouring positive patients, before results are available.

FebriDx (Lumos diagnostics, Sarasota, Florida, US) is a CE-marked lateral flow immunoassay POCT originally designed to differentiate between bacterial and viral respiratory infections by detecting two host response proteins, Myxovirus resistance protein A (MxA) and C-reactive protein (CRP), in finger-prick blood samples.[6](#_ENREF_6), [7](#_ENREF_7), [8](#_ENREF_8), [9](#_ENREF_9), [10](#_ENREF_10) MxA is a specific marker of interferon-induced antiviral host response. Studies performed during the first wave of the pandemic, demonstrated that MxA detection has high sensitivity and negative predictive value for identifying patients with COVID-19.[11](#_ENREF_11), [12](#_ENREF_12), [13](#_ENREF_13) FebriDx is a low-cost, analyser-free, easy-to-use POCT device and returns results in 10 minutes. As highlighted in a recent NICE Medtech briefing,[14](#_ENREF_14) FebriDx could be therefore be used to improve risk stratification of patients with suspected of COVID-19 in EDs; however, there have been no studies evaluating its clinical impact in this setting.

We sought to address this high-priority evidence gap by conducting an observational study evaluating the clinical impact of using FebriDx to improve the triage of patients with possible COVID-19 in our ED.

**Methods**

***Setting***

This single-centre retrospective observational study was conducted in the ED of the University Hospital Southampton NHS Foundation Trust (UK), a large acute teaching hospital serving a secondary care population of approximately 650,000 people. This study utilised routinely collected anonymised data. Study approval was granted by the University Hospital Southampton NHS Foundation Trust and the trust data protection office. Local research and development governance officers confirmed that research ethics committee review was not required.

***Intervention***

FebriDx is a self-contained lateral flow-based POCT that detects two host response proteins, CRP and MxA. Manufacturer instructions for use can be accessed at www.febridx.com/how-to-use#testing. Briefly, the patient’s skin is punctured by an integral lancet and 5 microliters of blood are drawn into the collection tube by placing it against a blood drop. Blood is then transferred to the lateral flow section of the device and reagents released by pressing a button. After 10 minutes, visual inspection reveals the presence or absence of three lines: a grey CRP line (top; detection threshold 20mg/L), a red MxA line (middle; detection threshold 40ng/ml), and a blue control line (bottom).[6](#_ENREF_6)

***Implementation***

Prior to this study, patients presenting to the ED were cohorted in the high-risk area solely based on the presence of risk factors for COVID-19 (any of the following: unexplained fever or fever with respiratory symptoms; new continuous cough; loss of sense of taste or smell; or known contact with a patient with confirmed COVID-19) OR a positive SARS-CoV-2 PCR test within the last 14 days.[15](#_ENREF_15) Patients who met any of these criteria were immediately moved to the high-risk cohort area and patients who did not were managed in lower-risk areas within the ED. The high-risk cohort area was a departmental area with limited bed space but with additional infection control precautions to prevent cross-infection, including floor-to-ceiling solid plastic screens between patient beds. Lower-risk areas of the ED had standard infection control precautions, including curtains between patient beds. Patients wore masks where possible and staff used personal protective equipment in line with Public Health England guidance in all areas.[16](#_ENREF_16) Patients remained in these cohort areas until either discharged home or admitted to speciality areas within the hospital (figure 1A).

Following a period of training and piloting, a FebriDx-based COVID-19 risk triage system was implemented in the ED on 22September 2020. Once patients with risk factors for COVID-19 arrived in the high-risk cohort area, trained personnel undertook the FebriDx test after obtaining verbal consent. Patients aged <18 years, with immunosuppression, symptom duration of more than 14 days, and patients without COVID-19 symptoms were not FebriDx tested because the diagnostic accuracy of FebriDx for identifying COVID-19 in these patient groups has not been established. Patients with confirmed COVID-19, diagnosed by PCR testing in the preceding 14 days, were also not FebriDx tested as per local protocols. After FebriDx results were available, patients who did not have a detectable antiviral host response (i.e. MxA-negative) were re-categorised as low risk for COVID-19, and were moved to lower-risk areas within the ED (figure 1B).

Patients with a detected antiviral host response (i.e. MxA-positive) remained in the high-risk cohort area and those who required hospital admission were then tested for SARS-CoV-2 and other respiratory viruses using rapid multiplex PCR testing. Patients who were SARS-CoV-2 PCR positive were transferred directly to COVID-19 positive wards, bypassing speciality assessment areas and reducing the risk of further exposure to other patients. Patients who required hospital admission with a negative MxA who were moved from the high-risk cohort area to lower-risk areas in the ED, were subsequently tested for SARS-CoV-2 using laboratory PCR when they arrived in the relevant speciality admissions area. In line with hospital policy, patients who were discharged from the ED were not routinely tested for SARS-CoV-2 by PCR, but were given advice about risk and isolation.

***Clinical data***

We reviewed routinely collected data on all patients managed in the high-risk cohort area and those managed in the ‘majors’ area (a lower-risk area for patients with major illness) in the ED during the study period. Data included: demographic data and comorbidities; times of arrival and transfer to different departmental areas; time patients left the department and their discharge destination; FebriDx results (if tested); and PCR results for SARS-CoV-2 (if tested).

***Outcome measures***

The primary outcome was the time FebriDx MxA-negative patients spent in the high-risk cohort area compared to MxA-positive patients. Secondary outcomes included: proportion of patients moved to low risk areas, the time patients spent in low risk areas within ED, total time spent in the ED, and time to PCR result, according to FebriDx result; the number and proportion of patients who were correctly and incorrectly moved to lower-risk ED areas based on subsequent SARS-CoV-2 PCR results; and the diagnostic accuracy (sensitivity, specificity, negative and positive predictive value and overall diagnostic accuracy) of FebriDx for COVID-19 compared to the reference standard of PCR.

***Statistical analysis***

Analysis was based on patient ‘episodes’ rather than individual patients – if the same patient attended the ED more than once during the study period, they were included in analyses again and counted as separate patient episodes. Analyses were carried out using Prism version 7.0 (GraphPad Software Inc., La Jolla, California). Baseline characteristics are summarised for FebriDx tested patients where data was available, and presented for all FebriDx tested patients and by FebriDx MxA result. The primary outcome measure was compared between FebriDx MxA-positive and MxA-negative patients using the Mann-Whitney U test. For the secondary outcomes, Mann-Whitney U test was used to compare continuous data (e.g. time to PCR result). Differences in median times and their 95% confidence intervals (CIs) were calculated using the Hodges–Lehmann estimate. Differences in proportions were assessed using chi-squared test or Fisher’s exact test, as appropriate depending on group size. For measures of diagnostic accuracy, sensitivity, specificity, predictive values and likelihood ratios were calculated for FebriDx MxA detection for the identification of COVID-19, compared with the reference standard of SARS-CoV-2 PCR. Time-to-event analysis data were analysed using the *lifelines* package in Python 3.7 and compared using the log-rank test. 95% CIs were calculated using Prism defaults.

**Results**

Between 22 September 2020 and 7 January 2021, 28,692 patients presented to the ED and 17,127 patients presented with major illness (presentations triaged to the majors section of the ED at arrival). 2171 (13%) fulfilled criteria for possible COVID-19 or were PCR positive for SARS-CoV-2 within the last 14 days and were therefore moved to the high-risk cohort area. 14,956 (87%) did not meet these criteria and were moved to lower-risk areas within the department. The flow of study participants in the study is shown in figure 2.

***Patient and departmental flow using FebriDx-based triage***

1321 (61%) of the 2171 patients triaged to the high-risk pathway were tested using FebriDx and 850 (39%) were not tested, due to the following reasons: PCR positive for SARS-CoV-2 with 14 days; FebriDx not indicated (due to immunosuppression, symptoms for more than 14 days, or the absence of COVID-19 symptoms); or unavailability of staff trained to perform FebriDx testing. The median time from presentation to ED and FebriDx testing was 30 (19 to 45) minutes. 17 (1.3%) of FebriDx tests had to be repeated due to absence of control line or operator error. Of those FebriDx tested, 217 (16%) of 1321 patients were MxA-positive and 1104 (84%) were MxA-negative. A higher proportion of FebriDx MxA-positive patients were male, of Asian ethnicity, and had cardiovascular disease or malignancy, compared to MxA-negative patients. Baseline demographic and clinical characteristics for all patients tested by FebriDx and according to result are shown in table 1. 865 (78%) of 1104 MxA-negative patients were moved from the high-risk cohort area to lower-risk areas within ED (the remainder stayed in the high-risk area) and 210 (97%) of 217 MxA-positive patients remained within the high-risk area for the duration of their stay in ED. Median (IQR) time spent in high-risk areas was 52 (34 to 92) minutes for FebriDx MxA-negative patients and 203 (142 to 255) minutes for FebriDx MxA-positive patients (difference of -134 minutes, 95%CI -144 to -122; p<0.0001). Time-to-event analysis for time to leaving the high-risk cohort area according to FebriDx result is shown in figure 3. The details of patients moved from the high-risk cohort area to lower-risk areas, and the time spent in each area, are shown in table 2.

***Comparison of risk factor-based and FebriDx-based COVID-19 risk triage algorithms, based on subsequent SARS-CoV-2 PCR results***

856 (65%) of the 1321 FebriDx tested patients (those initially triaged to the high-risk pathway) were admitted and subsequently had PCR testing for SARS-CoV-2. 5812 (39%) of the 14,956 patents who attended ED and did not have risk factors for COVID-19 (those initially triaged to the lower-risk pathway) were subsequently admitted and had PCR testing. Use of the previous risk factor-based triage algorithm (figure 1A), would have resulted in all 856 patients remaining in the high-risk cohort area; 153 (18%) of these 856 were subsequently PCR positive for SARS-CoV-2. 76 (1.3%) of 5812 patients triaged to the lower-risk areas in ED were subsequently SARS-CoV-2 positive (figure 4A).

Using the study FebriDx-based triage algorithm (figure 1B), compared to the risk factor-based algorithm, reduced the numbers of patients managed in the high-risk pathway from 856 to 339 (reduction of 60%, 95%CI 56 to 63). This allowed effective reconfiguration of clinical areas and other previously suspended ED services to re-commence. In addition, the FebriDx-based algorithm increased the proportion of SARS-CoV-2 PCR positive patients in the high-risk cohort area from 153 (18%) of 856 to 141 (42%) of 339 (difference of 24%, 95%CI 18 to 30; p<0.0001). The proportion of SARS-CoV-2 positive patients managed in the lower risk areas in ED (figure 4B) did not change with the FebriDx-based algorithm, 76 (1.3%) of 5812 versus 88 (1.4%) of 6329 (difference of 0.1, 95%CI -0.3 to 0.5; p=0.638).

***Diagnostic accuracy***

The prevalence of SARS-CoV-2 in the high-risk area over the study period was 153 (18%) of 856. Measures of diagnostic accuracy of FebriDx MxA detection for identification of COVID-19, compared to the reference standard of PCR, are shown in table 3.

Of the 29 patients who tested MxA-negative but were PCR-positive, 12 (43%) of 28 (missing data in 1 patient) had a low viral load (Ct value of >35 or equivalent); 12 (43%) of 28 (missing data in 1 patient) had a non-COVID-19 primary diagnosis on discharge summary; and 7 (24%) of 29 had a previous diagnosis of COVID-19 >14 days prior to the admission. The majority of patients, 16 (55%) of 29, had at least one of these factors.

**Discussion**

Delays that arise from waiting for confirmatory PCR-based diagnostic testing for COVID-19, coupled with limited side room availability, results in most UK hospitals cohorting patients together based on clinical likelihood of infection.[1](#_ENREF_1) This results in patients with non-COVID-19-related illness being initially managed within high-risk cohort areas alongside patients with COVID-19. Given that close indoor contact increases transmission rates,[17](#_ENREF_17), [18](#_ENREF_18), [19](#_ENREF_19), [20](#_ENREF_20) this increases the risk of COVID-19 nosocomial acquisition, which hinders the management of the epidemic and carries a high-risk of death.[2](#_ENREF_2), [3](#_ENREF_3) It is estimated that at least 14-24% of patients diagnosed with COVID-19 in UK hospitals have acquired the infection nosocomially [21](#_ENREF_21), [22](#_ENREF_22) and efforts to reduce transmission are therefore a national priority.

Our study assessed the clinical impact of the use of the FebriDx POCT as part of a triage tool for COVID-19 in the ED. We have demonstrated that the majority of patients with risk factors who are triaged to high-risk cohort areas do not, in fact, have COVID-19, even during a period of high prevalence. FebriDx was able to correctly identify the vast majority of these patients and allowed them to be rapidly moved out of high-risk cohort areas. Without the FebriDx testing algorithm, these patients would have remained in high-risk cohort areas for the duration of their ED stay until admitted or discharged, placing them at risk of nosocomial infection. Moving FebriDx MxA-negative patients out of the high-risk area significantly reduced overall patient numbers there and increased the proportion of PCR-positive patients within that area. This significantly improved departmental flow and allowed the limited number of high-risk patient beds to be used more appropriately.

In our study, FebriDx MxA had a high negative predictive value for COVID-19 (96%, 95%CI 94 to 97) compared with the reference standard of PCR, which is highly consistent with findings in our previously published diagnostic accuracy study.[11](#_ENREF_11) This high negative predictive value, despite the high prevalence of SARS-CoV-2 in this study, enables confident decision making in ED, allowing FebriDx MxA-negative patients to be rapidly moved from high-risk to lower-risk areas without waiting for the results of PCR testing. The lower sensitivity of 81% for FebriDx MxA compared with PCR may relate to the study including large numbers of frail elderly patients who did not have pneumonia and had low levels of RNA detected, likely representing persistent viral shedding from past infection.[23](#_ENREF_23) Although this resulted in small numbers of patients being moved to lower-risk areas and subsequently testing PCR positive for SARS-CoV-2, these patients are likely to represent a lower infective risk. Furthermore, the overall proportion of patients with COVID-19 managed in the lower-risk area was unchanged with and without FebriDx testing (1.4% vs 1.3% respectively).

For effective use in the emergency department, POCTs must yield rapid results in order to change patient management.[24](#_ENREF_24) Hence, even the relatively rapid turnaround times of many PCR-based point-of-care SARS-CoV-2 tests are too long to enable meaningful changes to ED pathways.[25](#_ENREF_25), [26](#_ENREF_26), [27](#_ENREF_27) FebriDx testing gives results within 10 minutes and we have shown that its rapid use is feasible in an ED setting. A proportion of patients in the high-risk cohort area were not tested by FebriDx for a variety of reasons, including absence of trained personnel or ineligibility, and this reflects the real-world nature of the study. Despite having no additional staff, the ED still tested over 60% of patients and move almost 80% of those with a negative result, demonstrating the use of a rapid test can lead to a change in patient pathways without additional resources. A similar recent study also used FebriDx as part of a triage algorithm for medical admissions and also found its use to be feasible, with a comparable high negative predictive value that resulted in a significant reduction in the need for isolation rooms.28

Our study had a number of limitations. As a non-randomised observational study, we cannot be sure that the changes seen following implementation were directly attributable to the FebriDx results, although this seems highly likely. Our study findings should ideally be confirmed in other studies and health economic evaluation should be performed. . Our study was conducted during a period of high prevalence for SARS-CoV-2 and it is uncertain whether the impact and diagnostic accuracy seen in this study would be maintained during periods of low COVID-19 prevalence, when the negative and positive predictive values would increase and decrease respectively. The need for this triage test may also be less in this circumstance because there are likely to be fewer patients presenting with high-risk symptoms. In addition, when there is increased co-circulation of other respiratory viruses the specificity is likely to be reduced. An additional limitation is that the majority of the patients discharged directly from the ED did not have a PCR test. This could alter the sensitivity and specificity if a different proportion of discharged patients had COVID-19, compared to those admitted. Lastly, although the impact of FebriDx on patient pathways in ED seen in this study suggest that its use would be associated with a reduction in nosocomial transmission, we were unable to measure this directly.

**Acknowledgements**

***Funding support***

This work was supported by University Hospital Southampton NHS Foundation Trust (UHSFT). The manufacturers of FebriDx (Lumos Diagnostics) had no input into the conception, design or conduct of this trial or the writing go the manuscript. The test kits were purchased at full price from a UK distributor by UHSFT.

***Conflicts of interest***

TWC has received speaker fees, honoraria, travel reimbursement, and equipment and consumables free of charge for the purposes of research outside of this submitted study, from BioFire diagnostics LLC and BioMerieux. TWC has received consultancy fees from Synairgen research Ltd, Randox laboratories Ltd and Cidara therapeutics. He a member of an advisory board for Roche and a member of two independent data monitoring committees for trials sponsored by Roche. He has acted as the UK chief investigator for an IMP study sponsored by Janssen. KB has received honoraria from Randox laboratories Ltd outside of this submitted study. All other authors declare they have no competing interests. All other authors declare they have no competing interests.

**Figure legends**

**Figure 1.** Emergency department COVID-19 risk triage algorithm prior to study (A; based on risk factors only) and during study (B; based on risk factors and FebriDx result). \*FebriDx testing was not undertaken in patients with immunosuppression, symptoms for more than 14 days, or with a positive SARS-CoV-2 PCR test within 14 days, and non-symptomatic COVID-19 contacts. These patients stayed in the high-risk cohort area until discharged or admitted.

**Figure 2.** Flow of participants.

**Figure 3.** Time-to-event curve for time to leaving high-risk cohort area, by FebriDx result.

**Figure 4.** Subsequent SARS-CoV-2 PCR-positivity of patients in each area of the emergency department, based on initial risk factor-based triage (A; hypothetical situation that would have occurred during the study period if FebriDx testing was not undertaken and patients were therefore not moved from the high-risk cohort area to lower risk areas) and FebriDx-based triage (B; actual situation during study, after patients were FebriDx tested and moved from the high-risk cohort area to lower risk areas based on the result). Of the patients in the high-risk cohort area, only those FebriDx tested were included.

**Tables**

**Table 1.** Baseline demographics and clinical characteristics for all FebriDx tested patients and by FebriDx MxA-result.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **All patients** **n=1321** | **MxA-positive patients****n=217** | **MxA-negative patients****n=1104** | **Between-group difference (95% CI)\*** | **p-value\*** |
| **Age, years** | 62 (40 to 78) | 63 (42 to 75) | 62 (38 to 79) | -1 (-4 to 3) | 0.865 |
| **Sex, n** | 1321 | 217 | 1104 |  |  |
|  **Male** | 672 (51) | 127 (59) | 545 (49) | -9 (-16 to -2) | **0.0143** |
|  **Female** | 649 (49) | 90 (41) | 559 (51) | - | - |
| **Ethnicity, n** | 1220 | 194 | 1026 |  |  |
|  **White British** | 1042 (85) | 155 (80) | 887 (86) | 7 (0 to 12) | **0.026** |
|  **White other** | 62 (5) | 10 (5) | 52 (5) | 0 (-3 to 5) | 1.0 |
|  **Black** | 10 (1) | 2 (1) | 8 (1) | 0 (-1 to 3) | 0.665 |
|  **Asian** | 75 (6) | 22 (11) | 53 (5) | -6 (-12 to -2) | **0.0028** |
|  **Other** | 31 (3) | 5 (3) | 26 (3) | 0 (-2 to 4) | 1.0 |
| **Comorbidities, n** | 976 | 163 | 813 |  |  |
|  **Hypertension** | 347 (36) | 65 (40) | 282 (35) | -5 (-14 to 3) | 0.211 |
|  **Diabetes** | 195 (20) | 39 (24) | 156 (19) | -5 (-13 to 2) | 0.165 |
|  **Cardiovascular disease** | 346 (35) | 77 (47) | 269 (33) | -14 (-23 to -6) | **0.0009** |
|  **Chronic respiratory disease** | 338 (35) | 49 (30) | 289 (36) | 5 (-2 to 14) | 0.207 |
|  **Chronic kidney disease** | 133 (14) | 27 (17) | 106 (13) | -4 (-11 to 2) | 0.230 |
|  **Chronic liver disease** | 42 (4) | 8 (5) | 34 (4) | -1 (-6 to 2) | 0.673 |
|  **Malignancy**  | 124 (13) | 29 (18) | 95 (12) | -6 (-13 to 0) | **0.039** |
|  **Dementia**  | 69 (7) | 8 (5) | 61 (8) | 3 (-7 to 8) | 0.314 |

All data are presented as n (%) or median (interquartile range). MxA, Myxovirus resistance protein. CI, Confidence interval. \*Between FebriDx MxA positive and negative groups

**Table 2.** Details of patient moves within the emergency department and time to PCR results for FebriDx MxA-positive and MxA-negative patients.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **MxA-positive patients****n=217)** | **MxA-negative patients****n=1104)** | **Difference\*****(95% CI)** | **p-value** |
| **Patients moved from high-risk cohort area to lower-risk areas of ED** | 7 (3%) | 865 (78%) | 75% (72% to 80%) | **<0.0001** |
| **Total time in ED, minutes** | 237 (200 to 329) | 231 (182 to 285) | -15 (-28 to -3) | **0.0022** |
| **Time in high-risk cohort area, minutes** | 203 (142 to 255) | 52 (34 to 92) | -134 (-144 to -122) | **<0.0001** |
| **Time in lower-risk areas of ED, minutes** | 0 (0 to 0) | 144 (68 to 203) | 129 (115 to 140) | **<0.0001** |
| **Time to PCR result, minutes** | 207 (143 to 301) | 322 (249 to 484) | 116 (93 to 140) | **<0.0001** |

All data are presented as n (%) or median (interquartile range). MxA, Myxovirus resistance protein. CI, Confidence interval. ED, emergency department. \*Differences in medians and 95%CI calculated using Hodges-Lehmann estimate.

**Table 3.** Measures of diagnostic accuracy of FebriDx MxA detection for identification of COVID-19, compared to the reference standard of PCR positivity, n = 856

|  |  |  |
| --- | --- | --- |
|  | **n/n** | **Value (95% CI)** |
| **Prevalence of COVID-19** | 153/856 | 18% (15 to 20) |
| **Sensitivity** | 124/153 | 81% (74 to 87) |
| **Specificity** | 661/703 | 94% (92 to 96) |
| **Positive predictive value** | 124/166 | 75% (69 to 80) |
| **Negative predictive value** | 661/690 | 96% (94 to 97) |
| **Positive likelihood ratio** | 0.81/0.06 | 13.6 (10.0 to 18.4) |
| **Negative likelihood ratio** | 0.19/0.94 | 0.20 (0.15 to 0.28) |
| **Overall accuracy** | 785/856 | 92% (90 to 93) |

**References**

1. Public Health England. COVID-19: Guidance for maintaining services within health and care settings. https://www.gov.uk/government/publications/wuhan-novel-coronavirus-infection-prevention-and-control. Date last updated: 21st January 2021. Date last accessed: 26th January 2021.

2. Rickman HM, Rampling T, Shaw K, et al. Nosocomial transmission of COVID-19: a retrospective study of 66 hospital-acquired cases in a London teaching hospital. *Clin Infect Dis* 2020; 72(4):690-693.

3. Khonyongwa K, Taori SK, Soares A, et al. Incidence and outcomes of healthcare-associated COVID-19 infections: significance of delayed diagnosis and correlation with staff absence. *J Hosp Infect* 2020; 106(4):663-672.

4. Brendish NJ, Poole S, Naidu VV, et al. Clinical impact of molecular point-of-care testing for suspected COVID-19 in hospital (COV-19POC): a prospective, interventional, non-randomised, controlled study. *Lancet Respir med* 2020; 8(12):1192-1200.

5. The Royal College of Emergency Medicine. COVID19: Resetting Emergency Department Care. www.rcem.ac.uk/RCEM/Quality\_Policy/Policy/COVID19\_Resetting\_Emergency\_Care/RCEM/Quality-Policy/Policy/COVID-19\_Resetting\_Emergency\_Care.aspx?hkey=1761be42-ed9f-4dc7-b82c-d19de402aae4. Date last accessed: January 10th 2021.

6. Self WH, Rosen J, Sharp SC, et al. Diagnostic Accuracy of FebriDx: A Rapid Test to Detect Immune Responses to Viral and Bacterial Upper Respiratory Infections. *J Clin Med* 2017; 6(10):94.

7. Shapiro NI, Self WH, Rosen J, et al. A prospective, multi-centre US clinical trial to determine accuracy of FebriDx point-of-care testing for acute upper respiratory infections with and without a confirmed fever. *Ann Med* 2018; 50(5):420-429.

8. Nakabayashi M, Adachi Y, Itazawa T, et al. MxA-based recognition of viral illness in febrile children by a whole blood assay. *Pediatr Res* 2006; 60(6):770-774.

9. Engelmann I, Dubos F, Lobert PE, et al. Diagnosis of viral infections using myxovirus resistance protein A (MxA). *Pediatrics* 2015; 135(4):e985-993.

10. Shirley M. FebriDx®: A Rapid Diagnostic Test for Differentiating Bacterial and Viral Aetiologies in Acute Respiratory Infections. *Mol Diagn Ther* 2019; 23(6):803-809.

11. Clark TW, Brendish NJ, Poole S, et al. Diagnostic accuracy of the FebriDx host response point-of-care test in patients hospitalised with suspected COVID-19. *J Infect* 2020; 81(4):607-613.

12. Karim N, Ashraf MZ, Naeem M, et al. Utility of the FebriDx point-of-care test for rapid triage and identification of possible coronavirus disease 2019 (COVID-19). *Int J Clin Pract* 2020; 75(3):e13702.

13. Urwin SG, Lendrem CB, Suklan J, et al. FebriDx point-of-care test in patients with suspected COVID-19: a pooled diagnostic accuracy study. MedRxiv (preprint), 2020.

14. FebriDx for C-reactive protein and myxovirus resistance protein A testing. Medtech innovation briefing [MIB224]. https://www.nice.org.uk/advice/mib224/chapter/Summary. Date last updated: 26th August 2020. Date last accessed: 29th Janurary 2021.

15. Public Health England. COVID-19: investigation and initial clinical management of possible cases. www.gov.uk/government/publications/wuhan-novel-coronavirus-initial-investigation-of-possible-cases/investigation-and-initial-clinical-management-of-possible-cases-of-wuhan-novel-coronavirus-wn-cov-infection. Date last updated: 2nd October 2020. Date last accessed: 29th Janurary 2021.

16. Public Health England. COVID-19: infection prevention and control (IPC). www.gov.uk/government/publications/wuhan-novel-coronavirus-infection-prevention-and-control Date last updated: 10th Janurary 2021. Date last accessed: 7th Janurary 2021.

17. Jayaweera M, Perera H, Gunawardana B, Manatunge J. Transmission of COVID-19 virus by droplets and aerosols: A critical review on the unresolved dichotomy. *Environ Res* 2020; 188:109819.

18. Islam MS, Rahman KM, Sun Y, Qureshi MO, Abdi I, Chughtai AA, Seale H. Current knowledge of COVID-19 and infection prevention and control strategies in healthcare settings: A global analysis. *Infect Control Hosp Epidemiol* 2020; 41(10):1196-1206.

19. Cevik M, Marcus JL, Buckee C, Smith TC. SARS-CoV-2 transmission dynamics should inform policy. *Clin Infect Dis* 2020; 73:S170-S176.

20. Meyerowitz EA, Richterman A, Gandhi RT, Sax PE. Transmission of SARS-CoV-2: A Review of Viral, Host, and Environmental Factors. *Ann Intern Med* 2021; 174(1):69-79.

21. Discombe M. Covid infections caught in hospital rise by a third in one week. www.hsj.co.uk/patient-safety/covid-infections-caught-in-hospital-rise-by-a-third-in-one-week/7029211.article. Date last updated: 18th December 2020. Date last accessed: 07th February 2021.

22. Discombe M. Over 450 people a day caught covid in hospitals during January. www.hsj.co.uk/coronavirus/over-450-people-a-day-caught-covid-in-hospitals-during-january/7029404.article. Date last updated: 29th Janurary 2021. Date last accessed: 07th February 2021.

23. Agarwal V, Venkatakrishnan AJ, Puranik A, et al. Long-term SARS-CoV-2 RNA shedding and its temporal association to IgG seropositivity. *Cell Death Discov* 2020; 6(1):138.

24. Brendish NJ, Malachira AK, Beard KR, Ewings S, Clark TW. Impact of turnaround time on outcome with point-of-care testing for respiratory viruses: a post hoc analysis from a randomised controlled trial. *European Respir J* 2018; 52(2):1800555.

25. Visseaux B, Le Hingrat Q, Collin G, et al. Evaluation of the QIAstat-Dx Respiratory SARS-CoV-2 Panel, the First Rapid Multiplex PCR Commercial Assay for SARS-CoV-2 Detection. *J Clin Microbiol* 2020; 58(8):e00630-20.

26. Smithgall MC, Scherberkova I, Whittier S, Green DA. Comparison of Cepheid Xpert Xpress and Abbott ID Now to Roche cobas for the Rapid Detection of SARS-CoV-2. *J Clin Virol* 2020; 128:104428.

27. Rhoads DD, Cherian SS, Roman K, Stempak LM, Schmotzer CL, Sadri N. Comparison of Abbott ID Now, DiaSorin Simplexa, and CDC FDA Emergency Use Authorization Methods for the Detection of SARS-CoV-2 from Nasopharyngeal and Nasal Swabs from Individuals Diagnosed with COVID-19. *J Clin Microbiol* 2020; 58(8):e00760-20.

28. Houston H, Deas G, Naik S, et al. Utility of the FebriDx point-of-care assay in supporting a triage algorithm for medical admissions with possible COVID-19: an observational cohort study. *BMJ Open* 2021; 11:e049179.