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Title:

Use of the FebriDx point-of-care assay as part of a triage algorithm for medical admissions with possible COVID-19

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Running Title: FebriDx triage for COVID-19

ABSTRACT

Objective: To evaluate a triage algorithm used to identify and isolate patients with suspected COVID-19 among medical patients needing admission to hospital using simple clinical criteria and the FebriDx assay.

Design: Retrospective observational cohort

Setting: Large acute NHS hospital in London, UK

Participants: All medical admissions from the emergency department between 10th August 2020 and 4th November 2020 with valid SARS-CoV-2 RT-PCR.

Interventions: Medical admissions were triaged as likely, possible or unlikely COVID-19 based on clinical criteria. Patients triaged as possible COVID-19 underwent FebriDx lateral flow assay on capillary blood, and those positive for MxA were managed as likely COVID-19.

Primary Outcome measures: Diagnostic accuracy (sensitivity, specificity and predictive values) of the algorithm and the FebriDx assay compared to SARS-CoV-2 RT-PCR from nasopharyngeal swabs as the reference standard.

Results: 4.0% (136) of 3,443 medical admissions had RT-PCR confirmed COVID-19. Prevalence of COVID-19 was 45.7% (80/175) in those triaged as likely, 4.1% (50/1,225) in possible and 0.3% (6/2,033) in unlikely COVID-19. Compared to SARS-CoV-2 RT-PCR, clinical triage had sensitivity of 95.6% (95%CI: 90.5% - 98.0%) and specificity of 61.5% (95%CI: 59.8% - 63.1%), whilst the triage algorithm including FebriDx had sensitivity of 92.6% (95%CI: 86.8% - 96.0%) and specificity of 86.4% (95%CI: 85.2% - 87.5%). The triage algorithm reduced the need for 2,859 patients to be admitted to isolation rooms. Ten patients missed by the algorithm had mild or asymptomatic COVID-19.

Conclusions: A triage algorithm including FebriDx assay had good sensitivity and was useful to 'rule-out' COVID-19 among medical admissions to hospital.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Pragmatic study including a large cohort of consecutive medical admissions receiving routine clinical care.
- A single SARS-CoV-2 RT-PCR is an imperfect reference standard for COVID-19.
- A higher prevalence of COVID-19 or other respiratory pathogens might alter performance of the FebriDx assay and triage algorithm.

INTRODUCTION

The Coronavirus disease (COVID-19) pandemic, caused by SARS-CoV-2, presents unprecedented challenges for infection prevention and control (IPC) within healthcare facilities worldwide.[1] Transmission may occur via respiratory droplet, fomite, or airborne routes (following aerosol-generating procedures).[1–3] Prolonged indoor contact increases transmission, and nosocomial transmission is common.[4,5] Respiratory isolation capacity (neutral or negative pressure side-rooms) is easily saturated within healthcare facilities.[6] Decisions to isolate patients in need of admission with suspected or possible COVID-19 must be rapid and accurate to maintain patient flow from emergency departments (EDs), yet minimise risk of nosocomial transmission.

As COVID-19 can present with non-specific symptoms, diagnostic confirmation is often sought by detection of SARS-CoV-2 ribonucleic acid (RNA) by reverse transcription-polymerase chain reaction (RT-PCR) from nasopharyngeal swab (NPS).[7] However, decisions about patient isolation from ED are usually required before the results of RT-PCR assays are available.[8,9] Even near-patient, rapid RT-PCR platforms with assay run times of 1-2 hours can be quickly overwhelmed, especially during peaks of COVID-19 incidence.[10,11] Multivariable diagnostic risk models, including clinical criteria and thoracic imaging, are not sufficient, but may be useful as a triage test to ration expensive or scarce point-of care assays.[12,13]

FebriDx (Lumos diagnostics, Sarasota, Florida, US) is a lateral flow assay that detects two host response proteins, Myxovirus resistance protein A (MxA, positive if >40ng/mL) and C-reactive protein (CRP, positive if >20mg/L) in capillary blood samples. MxA is an interferon-induced antiviral host response protein that has been studied as a biomarker to differentiate bacterial and viral respiratory infections.[14–17] More recently FebriDx has demonstrated a sensitivity of 93% and specificity of 86% for detecting COVID-19 compared to RT-PCR.[18] FebriDx could be useful as an early triage tool to identify patients with COVID-19 and help guide isolation and IPC in patients needing

admission to hospital.[18–21] We therefore developed and implemented a COVID-19 triage algorithm, supported by FebriDx, to inform patient flow from the ED whilst awaiting RT-PCR results. Here we describe the diagnostic performance of this algorithm compared to SARS-CoV-2 RT-PCR. We also describe the impact on isolation room demand and the time to FebriDx and RT-PCR results.

METHODS

Patient cohort

We utilised data prospectively entered into a COVID-19 triage database and retrospective extraction of clinical and bed allocation data from electronic patient records and hospital IT systems at Northwick Park Hospital, a large district general hospital serving a diverse population in North-West London. Patients were included if they required admission to a medical ward from the ED between 10th August 2020 and 4th November 2020 inclusive.

Consecutive medical admission were triaged into three categories for their likelihood of COVID-19 (unlikely, possible and likely) according to clinical features, observations and plain chest radiograph by the attending clinician based on Public Health England guidance (Table 1 and Supplementary Table 1).[22] Patients in the possible group underwent testing with FebriDx unless they declined, were immunosuppressed, required high dependency unit or intensive care unit (HDU/ICU) admission, had symptoms of COVID-19 for more than 10 days or had had COVID-19 previously. All patients underwent NPS testing with SARS-CoV-2 RT-PCR, with rapid RT-PCR assays being prioritised for patients in the likely group.

Patients with confirmed COVID-19 on SARS-CoV-2 RT-PCR, those triaged as likely, and those triaged as possible with a positive FebriDx or unable to have a FebriDx test were admitted to an isolation room or COVID-19 cohort area. Patients assigned to the unlikely COVID-19 group and those with a

negative FebriDx test were admitted to 'non-COVID' wards whilst awaiting SARS-CoV-2 RT-PCR results. Patients were excluded from the triage system if they were under sixteen years of age or admitted under specialities other than medicine.

FebriDx testing was implemented as part of routine clinical care in response to data on assay performance for COVID-19 and an urgent clinical need.[21] The study was approved by the London North West University Hospitals Trust Research and Development Committee (SE20/069), and given this was a retrospective review using routinely collected clinical data, they deemed formal ethical approval was not required. Results are reported in compliance with STARD and STROBE guidelines (see supplementary materials). The FebriDx tests were purchased independently from a UK distributer, and the manufacturer had no role in the study conception, design, data analysis or manuscript preparation. Due to the retrospective nature of this study, undertaken during the COVID-19 pandemic, patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Testing procedures and definitions

The FebriDx assay was performed as per the manufacturer's instructions at the point-of-care by ED health-care assistants following training. In brief, 5µL of capillary blood is placed on the sample window and reagents are released by pressing a button. The result is read after 10 minutes, with a positive result being the presence of a blue line in the control window and a red line in the MxA window (limit of detection 40ng/ml). The results from the CRP window were not used given all patients had laboratory CRP measurements. Staff performing FebriDx had access to clinical information but not SARS CoV-2 RT-PCR results at the time of FebriDx testing. Routine SARS CoV-2 RT-PCR was done on NPS using either the Panther Fusion SARS-CoV-2 (Hologic Inc, CA, USA), Abbott RealTime SARS-CoV-2(Abbott Park, IL, USA) or an extraction-free SARS-CoV-2 RT-PCR assay

developed by Health Services Laboratories (HSL), UK.[23] Rapid RT-PCR assays used were Xpert Xpress SARS-CoV-2 (Cepheid, CA, USA) or SAMBA II SARS-CoV-2 (Diagnostics for the Real World, CA, USA).

Patients were defined as having COVID-19 or not based on the first valid RT-PCR result up to 72 hours after admission. Patients without a valid RT-PCR result or triage status were excluded from the analysis. Vital signs, including National Early Warning Score (NEWS) were recorded on arrival to the ED. All biochemical, haematological and radiological data were from the first results within 48 hours of admission. Thoracic imaging (chest radiographs and CT) were reported and coded based upon guidelines on COVID-19 from the British Society of Thoracic Imaging (BSTI) at the time of reporting by radiologists.[24] Vital status is reported at the time of hospital discharge or data extraction (20th November 2020) for those who were still inpatients.

Data Analysis and Statistical Methods

We calculated the proportion of patients with confirmed COVID-19 in each triage category, and the diagnostic accuracy (sensitivity, specificity, and positive and negative predictive values with 95% confidence intervals) of both the triage algorithm overall, and the FebriDx assay in patients with possible COVID-19 compared to a SARS-CoV-2 RT-PCR reference standard. Patients with missing RT-PCR or those missing data on triaging were excluded from analysis. We also reported time to FebriDx testing and valid RT-PCR testing. We described the proportion of patients with COVID-19 who were correctly isolated, estimated the number of isolation beds made available by FebriDx testing, and described the patients with COVID-19 who were incorrectly triaged by the algorithm. Basic descriptive statistics were performed, with comparisons made using chi-squared tests for proportions, t-tests for means and Wilcoxon rank sum for medians. Logistic regression was used to compare age and sex adjusted estimates of in-hospital death in each triage group, using complete cases only. Statistical analyses were performed using Stata version 14.0 (StataCorp, LLC, College

Station TX). Based on an anticipated sensitivity of 93%, a sample size of 3335 would estimate the sensitivity of the triage algorithm ±5% with alpha 0.05 and prevalence of 3%.

RESULTS

Baseline characteristics and COVID-19 diagnosis

Between the 10th August and 4th November 2020, there were 9,645 emergency department attendances resulting in further hospital care. Of these, 3,433 (35.6%) were adult medical patients admitted for further treatment, were triaged using the algorithm based on COVID-19 status and had a valid SARS-CoV-2 RT-PCR result (figure 1). 175 (5.1%) patients were triaged as likely COVID-19, 2,033 (59.2%) patients as unlikely and 1,225 (35.7%) patients were triaged into the possible COVID-19 category. Key patient characteristics are given in Table 2.

There were several differences between the three triage groups (Table 2). The likely COVID-19 group were younger and more unwell at admission (NEWS of 5 vs 1 for patients in the unlikely group, p<0.001) and more frequently required supplemental oxygen (30.4% compared to 2.1% in the unlikely [p<0.001], and 20.4% in the possible group [p=0.003]). As expected, more patients in the likely COVID-19 group had chest radiograph changes typical for COVID-19 than in the other groups (38.3% compared to 2.3% in possible [p<0.001], and 0.3% in unlikely [p<0.001]). The possible COVID-19 group were older (median 75 years [IQR: 60 – 84]) than the other two groups and were more likely to have an elevated neutrophil count (greater than 7.5x10^9/l) than the likely or possible groups.

Overall, 136/3,443 admissions (4.0%) were diagnosed with PCR-confirmed COVID-19. Prevalence of COVID-19 was 45.7% (80/175) in likely patients, and 4.1% (50/1,225) in the possible group. Of those triaged as unlikely COVID-19, only 6/2,033 (0.3%) were SARS-CoV-2 RT-PCR positive.

Performance of FebriDx and triage algorithm

The overall diagnostic performance of the clinical triage algorithm compared to the gold standard of SARS-CoV-2 RT-PCR is summarised in table 3 and supplementary table 2. 958 (78.2%) patients in the

possible group were tested using FebriDx (those excluded are detailed in figure 1). 13.8% (132/958) of FebriDx test results were positive for MxA, with 86.2% negative and no invalid results. The median duration of COVID-19 symptoms in patients tested by FebriDx was 2 days (IQR 1-3, n=847). Patients with positive FebriDx results were younger, more likely to be febrile and less likely to have raised neutrophil counts than FebriDx negative patients (supplementary table 3).

31.1% (41/132) of patients with a positive FebriDx had a positive SARS-CoV-2 RT-PCR, whilst only 4/826 (0.5%) with a negative FebriDx were diagnosed as having COVID-19. All 4 patients with false-negative FebriDx results had normal chest radiographs. 2 patients tested negative for COVID-19 by SARS-CoV-2 RT-PCR but had positive FebriDx results and chest radiograph appearances typical for COVID-19. In the possible COVID-19 group, FebriDx results were available a median of 2.2 hours (IQR: 1.4 to 3.1, n=808) and RT-PCR results a median of 17.8 hours (IQR: 11.35 – 25.34, n=456) after arrival to the ED (figure 2). 88.0% of FebriDx results were available within 4 hours of arrival (n=808).

The triage algorithm correctly identified 126/136 patients with PCR-confirmed COVID-19 in the likely group (sensitivity 92.6%, 95%CI: 86.8 - 96.0) (table 3). The 10 patients who were SARS-CoV-2 RT-PCR positive but missed by the triage algorithm are described in supplementary table 4. 6/10 were classified as unlikely, and 4/10 were classified as possible COVID-19 and had a negative FebriDx. 2/10 were febrile on admission, none required supplemental oxygen, length of stay was short (median 2 days) and 8/8 had normal chest radiographs (2 did not have thoracic imaging done). Specificity of the algorithm was 86.4% (85.2 - 87.5), and negative predictive value was 99.7% (99.4 - 99.8).

Outcomes

94.9% (129/136) of patients with COVID-19 were appropriately managed in isolation rooms as a result of the triage algorithm (supplementary table 5). Of the 10 patients with PCR-confirmed COVID-19 not identified by the triage algorithm, only 7 were not managed in an isolation room. Had

all patients been isolated until SARS-CoV-2 RT-PCR result was available (ie without using any triage algorithm) 2,859 more isolation rooms would have been used. The FebriDx assay allowed 826 more patients to be managed in 'non-COVID' areas than if all patients triaged possible COVID-19 had required isolation (9.5 isolation rooms saved per day).

11 (8.1%) patients with COVID-19 died compared to 150 (4.5%) without COVID-19 (p=0.042). Age and sex adjusted odds of death during the admission were higher for patients in the likely (OR: 3.42, 95% CI: 1.81 - 6.45) and possible groups (OR: 2.44, 95% CI: 1.73 - 3.44) than the unlikely COVID-19 group.

DISCUSSION

Our main findings are that a pragmatic triage algorithm using simple clinical parameters available within the ED and the FebriDx point-of-care test had good sensitivity (92.6%) and excellent NPV (99.7%) for COVID-19 diagnosed by RT-PCR. Inclusion of FebriDx improved the specificity of triage with minimal reductions in sensitivity, allowing a substantial reduction in the number of isolation rooms needed.

Although clinicians were able to identify patients likely and unlikely to have COVID-19 (45.7% and 0.3% of whom had confirmed COVID-19 respectively) based on clinical assessment, radiology and basic blood tests, their assessment was not sufficiently specific. Patients identified as 'possible' COVID-19 still had a 4% prevalence of COVID-19, and were a large enough group to overwhelm isolation room capacity. We demonstrate a simple, rapid test performed at the point-of-care can help further risk stratify this group. In real-life settings in a busy ED, a point-of-care test was able to inform isolation decisions within 4 hours of arrival compared to PCR results which were too slow to inform patient flow from ED, even when using 'rapid' PCR assays. Although formal cost-effectiveness analysis was not performed, each FebriDx test only costs about US$18, and this may lead to cost savings.

The strengths of this study are its pragmatic design under routine clinical settings, and that we are able to account for over 95% of medical admissions, reducing risks of bias. There are, however, several limitations. A single SARS-CoV-2 RT-PCR is an imperfect reference standard, and does not account for RT-PCR negative COVID-19 patients. We used multiple RT-PCR platforms, which will have different PCR targets and performance. 10% of patients in the possible group did not get tested with FebriDx for unclear reasons, potentially introducing bias. The prevalence of COVID-19 was 4% in this cohort, and it is unclear what impact a higher prevalence of COVID-19 or other respiratory

pathogens such as influenza would have on these findings. The criteria for likely and possible COVID-19 groups changed subtly during the study period, although this is unlikely to significantly alter the outcomes.

These data build on previous studies of FebriDx showing good sensitivity, and utility as a 'rule-out' test for COVID-19.[17–20] We may have underestimated the sensitivity by not testing those patients deemed most likely to have COVID-19, although testing this group would have been unlikely to alter clinical decisions, even if FebriDx negative, given the high pre-test probability. The FebriDx test allowed patients with possible COVID-19 to be divided into two groups with similar characteristics and clinical features, but vastly different COVID-19 prevalence (0.5% in FebriDx negative, and 31.1% in FebriDx positive). However, about 10% of patients in this group were not eligible for FebriDx testing.

Only ten patients with COVID-19 were incorrectly triaged by the algorithm, four of whom were tested and 'missed' using FebriDx. These patients were younger, less symptomatic, did not have chest radiograph changes, and mostly likely had mild or asymptomatic COVID-19 infection. Given that MxA is an intracellular GTPase induced by type I and type III interferon responses, it is plausible that sensitivity would be lower in pauci- or asymptomatic infection.[25] Although the patients missed by the algorithm are potential sources of nosocomial transmission, asymptomatic disease is thought to be less transmissible.[26] We found no nosocomial cases related to these patients.

In conclusion, we demonstrate a simple triage system including the novel FebriDx point-of-care test had good sensitivity and negative predictive value for COVID-19 and utility for managing medical admissions from the ED.

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Author contributions

HH, AGW, LJ, SF, JBL, JR, N Vaughan, N Vaid, GGR, and AKA made substantial contribution to the conception of the work. HH, AGW, LJ, and GD made substantial contribution to the design of the work. HH, GD, SN, KS, SP, MGD, and MT contributed to data acquisition. HH and AGW analysed the data. HH, AGW and LJ contributed to data interpretation. HH and AGW drafted the manuscript. All authors contributed to revising the manuscript critically for important intellectual content, approved the final manuscript and are accountable for all aspects of the work.

Competing interests statement

The authors have no competing interests to declare.

Data availability statement

Data are available upon reasonable request, subject to approval by the London North West University Healthcare NHS Trust Research and Governance Department and approval from relevant ethics and regulatory bodies.

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Tables

COVID-19 triage category	**Clinical Criteria**	**Diagnostics performed in ED**	**Bed Allocation from ED**
Likely	Recent Contact with a confirmed COVID-19 case OR Travel to High Risk country within the last 14 days	Routine RT-PCR	Isolation Room
	Known COVID-19 illness confirmed prior to current attendance	Urgent RT-PCR	COVID-19 cohort area or isolation room
	High Clinical Suspicion (eg. Oxygen Requirement, Bilateral infiltrates, Normal WCC/high CRP) OR Change in Normal sense of Smell or Taste		Isolation Room
Possible	Clinical or Radiological Pneumonia OR Fever / Persistent Cough / Shortness of Breath / Hypoxia / Diarrhoea / Confusion	FebriDx * & Urgent RT-PCR	Isolation Room if FebriDx Positive
			Non-COVID Area if FebriDx Negative
Unlikely	None of the Above	Routine RT-PCR	Non-COVID Area

Table 1. Clinical Criteria for determining triage groups, testing strategy and bed allocation from the Emergency Department prior to RT-PCR result. Clinical criteria for determining triage groups are shown as of 08/10/2020. Changes to these criteria over time are detailed in supplementary table 1. * Patients were excluded from FebriDx testing if they had a prior history of COVID-19, were immunosuppressed, required intensive care or high dependency unit admission, or had had COVID-19 symptoms for > 10 days. RT-PCR=Reverse transcription polymerase chain reaction, ED=Emergency department

Variable	Unlikely	Possible	Likely	P-value*
N	2033	1225	175	
Age (years) median (IQR)	69 (49, 82)	75 (60, 84)	62 (48, 74)	<0.001
Age over 65 years, n (%, 95%CI)	1128 (55.5%, 53.3; 57.6)	846 (69.1%, 66.5; 71.6)	79 (45.1%, 37.8; 52.5)	<0.001
Female Sex, n (%, 95%CI)	969 (47.7%, 45.5; 49.8)	603 (49.2%, 46.4; 52.0)	72 (41.1%, 33.9; 48.4)	0.045
Male Sex, n (%, 95%CI)	1064 (52.3%, 50.2; 54.5)	622 (50.8%, 48.0; 53.6)	103 (58.9%, 51.6; 66.1)	
NEWS, median (IQR)	1 (0, 3)	4 (2, 6)	5 (3, 7)	0.017
Respiratory Rate (breaths/min), median (IQR)	18 (18, 20)	24 (20, 28)	24 (21, 32)	<0.001
SpO2 <94%, n (%, 95%CI)	61 (3.1%, 2.4; 3.9)	234 (19.5%, 17.3; 21.8)	38 (22.2%, 16.0; 28.5)	0.41
Required Supplemental Oxygen, n (%, 95%CI)	52 (2.7%, 2.0; 3.4)	245 (20.4%, 18.1; 22.7)	52 (30.4%, 23.5; 37.3)	0.003
Temperature >37.5ºC, n (%, 95%CI)	172 (8.8%, 7.6; 10.1)	359 (30.0%, 27.4; 32.6)	73 (42.7%, 35.3; 50.1)	<0.001
Chest Radiograph - Normal, n (%, 95%CI)	1171 (81.0%, 79.0; 83.0)	537 (49.9%, 46.9; 52.9)	42 (29.8%, 22.2; 37.3)	<0.001
Chest Radiograph - Typical for COVID-19, n (%, 95%CI)	4 (0.3%, 0.0; 0.5)	25 (2.3%, 1.4; 3.2)	54 (38.3%, 30.3; 46.3)	<0.001
Chest Radiograph - Other, n (%, 95%CI)	271 (18.7%, 16.7; 20.8)	514 (47.8%, 44.8; 50.8)	45 (31.9%, 24.2; 39.6)	<0.001
Chest CT - Normal, n (%, 95%CI)	8 (23.5%, 9.3; 37.8)	9 (16.4%, 6.6; 26.1)	0 (0.0%, 0.0; 0.0)	0.25
Chest CT - Typical for COVID-19, n (%, 95%CI)	0 (0.0%, 0.0; 0.0)	3 (5.4%, -0.5; 11.5)	3 (42.9%, 6.2; 79.5)	0.002
Chest CT - Other, n (%, 95%CI)	26 (76.5%, 62.2; 90.7)	43 (78.2%, 67.3; 89.1)	4 (57.1%, 20.5; 93.8)	0.22
CRP (mg/L), median (IQR)	5.7 (1.4, 26.9)	26.4 (7.05, 87.65)	53.7 (25.9, 122.7)	<0.001
CRP >20mg/L, n (%, 95%CI)	545 (28.7%, 26.7; 30.7)	656 (55.8%, 52.9; 58.6)	134 (80.2%, 74.2; 86.3)	<0.001
Lymphocyte Count <1.0x10^9/l, n (%, 95%CI)	373 (25.3%, 23.1; 27.5)	383 (43.9%, 40.6; 47.2)	70 (54.7%, 46.1; 63.3)	0.022
Neutrophil Count >7.5x10^9/l, n (%, 95%CI)	620 (32.0%, 29.9; 34.0)	598 (50.4%, 47.6; 53.3)	61 (36.1%, 28.9; 43.3)	<0.001
Crude In Hospital Mortality, n (%, 95%CI)	57 (2.8%, 2.1; 3.6)	89 (7.5%, 6.0; 9.0)	13 (7.8%, 3.7; 11.8)	0.89
SARS-CoV-2 RNA Detectable on RT-PCR, n (%, 95%CI)	6 (0.3%, 0.1; 0.5)	50 (4.1%, 3.0; 5.2)	80 (45.7%, 38.3; 53.1)	<0.001

Table 2: Baseline characteristics, vital signs, initial investigations, mortality and SARS-CoV-2 RT-PCR results for patients in the unlikely, possible and likely COVID-19 groups. For observations on arrival, 3.2 to 4.1% of data were missing. Data were missing for 5.5% of CRP results and 4.0% of haematology results, 22.4% of chest radiograph reports and 2.1% of discharge outcomes. 96 patients (2.8%) had a chest CT report available. Imaging reports were coded as per BSTI guidelines. Chest Radiograph reports were coded as: CVCX0 = Normal; CVCX1 = Classic; CVCX2 = Indeterminate; CVCX3 = Non-COVID-19. Chest CT reports were coded as: CVCT0= Normal; CVCT1= Classic/probable; CVCT2= Indeterminate; CVCT3= Non-COVID-19. Pair-wise comparisons were performed using chi-squared tests for proportions, t-tests for means and Wilcoxon rank sum for median. *P-values are shown for the comparison between the possible and likely COVID-19 groups IQR=Inter-quartile range, CI=Confidence Interval, NEWS=National Early Warning Score, SpO2=Oxygen Saturations, CRP=C-Reactive Protein, CT=Computerised Tomography

	Algorithm with FebriDx (n = 3433)		Algorithm without FebriDx (n=3433)		FebriDx only (n = 958)	
	n/N	% (95%CI)	n/N	% (95%CI)	n/N	% (95%CI)
Sensitivity	126 / 136	92.6 (86.8 - 96.0)	130 / 136	95.6 (90.5 – 98.0)	41 / 45	91.1 (78.4 - 96.7)
Specificity	2849 / 3297	86.4 (85.2 - 87.5)	2027 / 3297	61.5 (59.8 – 63.1)	822 / 913	90.0 (87.9 - 91.8)
Negative Predictive Value	2849 / 2859	99.7 (99.4 - 99.8)	2027 / 2033	99.7 (99.3 – 99.9)	822 / 826	99.5 (98.7 - 99.8)
Positive Predictive Value	126 / 574	22.0 (18.8 - 25.5)	130 / 1400	9.3 (7.9 – 10.9)	41 / 132	31.1 (23.7 - 39.5)

Table 3 Measures of Diagnostic Performance for the Triage Algorithm (with and without FebriDx) and FebriDx assay alone for the detection of COVID-19, compared to the reference standard of SARS-CoV-2 RT-PCR. Diagnostic performance measures are shown for three tests: the triage algorithm including the FebriDx test, the whole triage algorithm without FebriDx (ie patients in the likely or possible group classified as likely COVID-19, and for FebriDx alone. A cross-tabulaiton of positive and negative test results and reference standard are presented in supplementary table 2. CI = Confidence Interval

Figure Legends:

Figure 1: Patient flow through the study and the COVID-19 triage algorithm
Patients were included if they required admission to a medical ward from the ED between 10th August 2020 and 4th November 2020 inclusive. Patients were excluded if they were under sixteen years of age, admitted under specialities other than medicine, or if their triage status or SARS-CoV-2 RT-PCR result was unknown. PCR = SARS-CoV-2 RT-PCR.

Figure 2: Time from arrival to the availability of FebriDx and SARS-CoV-2 RT-PCR results
Kernel frequency density plot using the Epanechniko function; Time to FebriDx result was calculated as the time from arrival to the emergency department until the time the FebriDx result was recorded (blue plot), bandwidth=0.3; Time to RT-PCR result was calculated as the time from arrival to to the emergency department until the time the SARS-CoV-2 RT-PCR result was recorded (red plot), bandwidth=2.

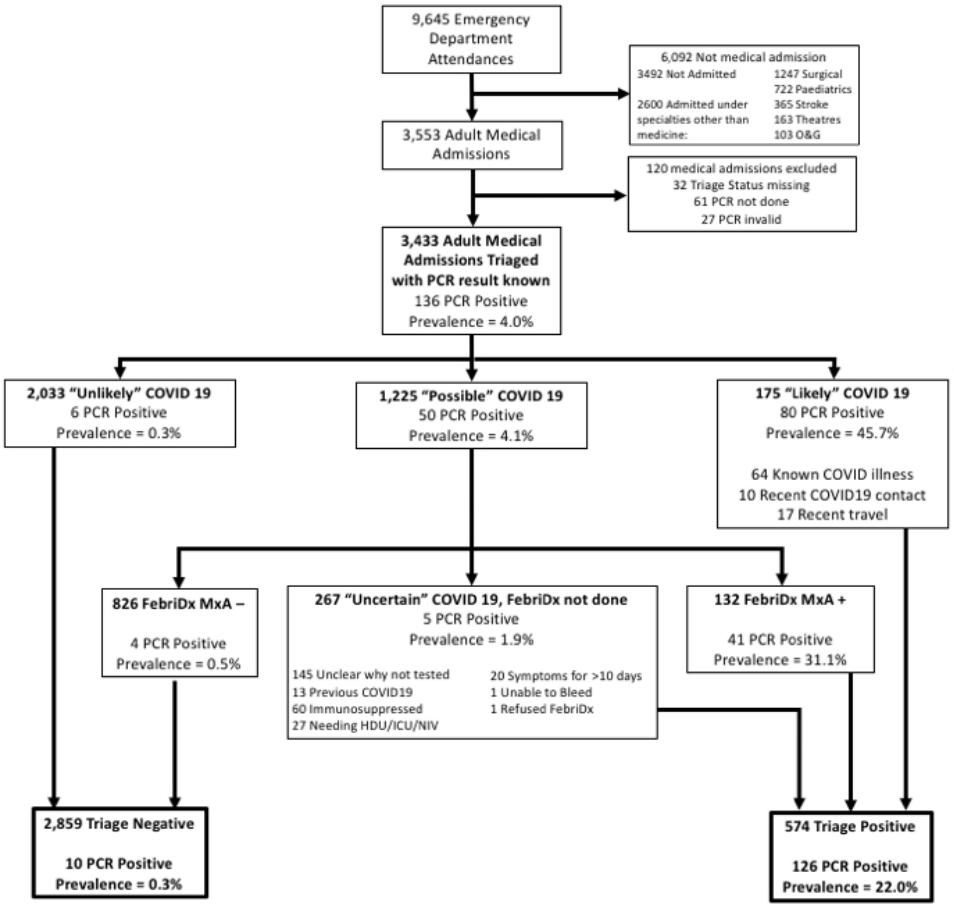

Figure 1

494x494mm (37 x 37 DPI)

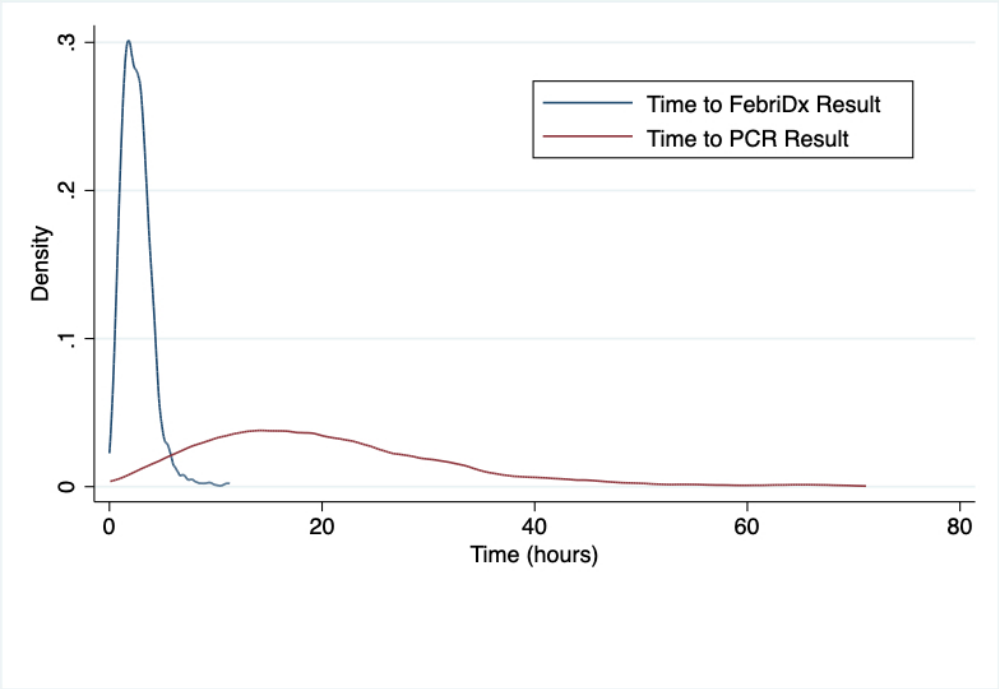

Figure 2

276x191mm (72 x 72 DPI)

Use of the FebriDx point-of-care assay as part of a triage algorithm for medical admissions with possible COVID-19

Supplementary Tables:

Supplementary Table 1: Changes made to the inclusion criteria for the triage categories and the exclusion criteria for FebriDx testing during the study period.

<table>
<tr><td></td><td colspan="4">Date of Update to COVID-19 Triage Criteria</td></tr>
<tr><td></td><td>06/07/2020</td><td>09/09/2020</td><td>21/09/2020</td><td>08/10/2020</td></tr>
<tr><td rowspan="5">Likely</td><td colspan="4">Confirmed COVID-19 during current illness</td></tr>
<tr><td colspan="4">High Clinical Suspicion
(eg. Oxygen Requirement, Bilateral infiltrates, Normal WCC/high CRP)</td></tr>
<tr><td colspan="4">Recent Contact with a confirmed COVID-19 case</td></tr>
<tr><td colspan="4">Travel to High Risk country within the last 14 days</td></tr>
<tr><td colspan="3"></td><td>Change in Normal sense of Smell or Taste</td></tr>
<tr><td rowspan="4">Possible</td><td colspan="3">Change in Normal sense of Smell or Taste</td><td></td></tr>
<tr><td colspan="4">Clinical or Radiological Pneumonia</td></tr>
<tr><td colspan="2">Fever PLUS Persistent Cough OR Shortness of Breath OR Hypoxia</td><td colspan="2">Fever OR Persistent Cough OR Shortness of Breath OR Hypoxia</td></tr>
<tr><td colspan="3"></td><td>Confusion OR Diarrhoea</td></tr>
<tr><td>Unlikely</td><td colspan="4">None of the Above</td></tr>
<tr><td rowspan="4">Exclusion Criteria for FebriDx</td><td colspan="4">Immunosuppressed</td></tr>
<tr><td colspan="4">Previous COVID-19</td></tr>
<tr><td></td><td colspan="3">Requiring ITU/HDU/NIV</td></tr>
<tr><td colspan="2"></td><td colspan="2">COVID-19 Symptoms >10 days</td></tr>
</table>

Supplementary Table 1 footnotes:
The inclusion criteria for the triage categories and the exclusion criteria for FebriDx testing were adjusted during the course of this pragmatic study. WCC=white cell count, CRP= C-Reactive Protein, ITU=Intensive Therapy Unit, HDU=High Dependency Unit, NIV=Non-Invasive ventilation.

Supplementary Table 2:

A		SARS-CoV-2 RT-PCR		
		Positive	Negative	Total
Algorithm with FebriDx (n=3433)	Positive	126	448	574
	Negative	10	2849	2859
	Total	136	3297	3433

B		SARS-CoV-2 RT-PCR		
		Positive	Negative	Total
Algorithm without FebriDx (n=3433)	Positive	130	1270	1400
	Negative	6	2027	2033
	Total	136	3297	3433

C		SARS-CoV-2 RT-PCR		
		Positive	Negative	Total
FebriDx only (n=958)	Positive	41	4	45
	Negative	4	822	826
	Total	45	913	958

Table 4 footnotes: Cross tabulation of results of the triage algorithm with FebriDx (A) and without FebriDx (B) as well as the results of FebriDx within the possible COVID-19 group receiving a FebriDx test (C) compared to a SARS-CoV-2 RT-PCR reference standard.

Supplementary Table 3: Baseline characteristics, vital signs, initial investigations, mortality and SARS-CoV-2 RT-PCR results for patients in the possible COVID-19 group by FebriDx test result

Variable	FebriDx Negative	FebriDx Positive	FebriDx Not Done	FebriDx Positive vs Negative
N	826	132	267	
Age (years) median (IQR)	77 (61, 85)	69.5 (54.5, 81.5)	72 (60, 81)	<0.001
Age over 65 years, n (%, 95%CI)	586 (70.9, 67.8; 74.0)	80 (60.6, 52.0; 68.6)	180 (67.4, 61.5; 72.8)	0.017
Female Sex, n (%, 95%CI)	399 (48.3, 44.9; 51.7)	63 (47.7, 39.3; 56.3)	141 (52.8, 46.8; 58.8)	0.90
Male Sex, n (%, 95%CI)	427 (51.7, 48.3; 55.1)	69 (52.3, 43.7; 60.7)	126 (47.2, 41.2; 53.2)	
NEWS, median (IQR)	4 (2, 7)	4 (3, 6)	4 (2, 6)	0.62
Respiratory Rate (breaths/min), median (IQR)	24 (20, 28)	24 (20, 28)	24 (19, 28)	0.74
SpO2 <94%, n (%, 95%CI)	164 (20.2, 17.6; 23.1)	24 (18.6, 12.8; 26.3)	46 (17.9, 13.7; 23.1)	0.67
Required Supplemental Oxygen, n (%, 95%CI)	170 (20.9, 18.2; 23.8)	21 (16.3, 10.8; 23.7)	54 (21.0, 16.4; 26.5)	0.23
Temperature >37.5ºC, n (%, 95%CI)	245 (30.2, 27.1; 33.4)	55 (42.6, 34.4; 51.4)	59 (23.0, 18.3; 28.6)	0.005
Chest Radiograph - Normal, n (%, 95%CI)	375 (51.2, 47.6; 54.9)	52 (43.3, 34.7; 52.4)	110 (49.1, 42.6; 55.7)	<0.001
Chest Radiograph - Typical for COVID-19, n (%, 95%CI)	8 (1.1, 0.6; 2.2)	11 (9.2, 5.1; 15.8)	6 (2.7, 1.2; 5.9)	<0.001
Chest Radiograph - Other, n (%, 95%CI)	349 (47.7, 44.1; 51.3)	57 (47.5, 38.7; 56.5)	108 (48.2, 41.7; 54.8)	0.97
Chest CT - Normal, n (%, 95%CI)	9 (19.6, 10.2; 34.1)	0 (0)	0 (0)	0.40
Chest CT - Typical for COVID-19, n (%, 95%CI)	2 (4.4, 1.0; 16.5)	0 (0)	1 (16.7, 0.9; 81.4)	0.71
Chest CT - Other, n (%, 95%CI)	35 (76.1, 61.1; 86.5)	3 (100)	5 (83.3, 18.6; 99.1)	0.34
CRP (mg/L), median (IQR)	26.3 (6.5, 95.5)	37.05 (17.1, 78.9)	18.85 (4.9, 76.3)	0.012
CRP >20mg/L, n (%, 95%CI)	443 (55.9, 52.5; 59.4)	87 (66.9, 58.4; 74.5)	126 (49.6, 43.5; 55.8)	0.019
Lymphocyte Count <1.0x10^9/l, n (%, 95%CI)	263 (43.8, 39.9; 47.8)	46 (47.9, 38.1; 57.9)	74 (41.8, 34.7; 49.2)	0.455
Neutrophil Count >7.5x10^9/l, n (%, 95%CI)	422 (52.8, 49.3; 56.3)	50 (38.5, 30.5; 47.1)	126 (49.0, 42.9; 55.2)	0.002
Mortality, n (%, 95%CI)	65 (8.1, 6.4; 10.2)	6 (4.7, 2.1; 10.2)	18 (6.9, 4.4; 10.8)	0.19
SARS-CoV2 RNA Detectable on RT-PCR, n (%, 95%CI)	4 (0.5, 0.3; 1.3)	41 (31.1, 23.7; 39.5)	5 (1.9, 0.8; 4.4)	<0.001

Supplementary Table 2 footnotes: Missing data are summarised in the footnotes to table 2 in the main text. Imaging reports were coded as per BSTI guidelines. Chest Radiograph reports were coded as: CVCX0 = Normal; CVCX1 = Classic; CVCX2 = Indeterminate; CVCX3 = Non-COVID-19. Chest CT reports were coded as: CVCT0= Normal; CVCT1= Classic/probable; CVCT2= Indeterminate; CVCT3= Non-COVID-19. IQR=Inter-quartile range, CI=Confidence Interval, NEWS=National Early Warning Score, SpO2=Oxygen Saturations, CRP=C-Reactive Protein, CT=Computerised Tomography

Supplementary Table 4: Baseline characteristics of patients with positive SARS-CoV-2 RT-PCR results who were classified as triage negative by the algorithm

Case	1	2	3	4	5	6	7	8	9	10
Triage Status	Unlikely						FebriDx Negative			
Decade of Life*	5	7	3	5	7	6	6	3	7	5
Sex (F/M)	F	M	F	M	M	M	F	M	F	F
Presentation	Fever and epigastric pain	Hypoglycaemic collapse	Hyperkalaemia on clinic bloods	Herpes Zoster	Intentional Overdose	Unstable Angina	URTI symptoms	Diarrhoea	Fever and SOB	Headache and anosmia
Duration of Symptoms (days)	x	x	x	x	x	x	5	7	1	2
NEWS on Arrival	4	1	0	1	2	1	7	2	3	3
Respiratory Rate (breaths/min)	20	18	18	20	14	18	32	18	22	21
SpO2 (%)	97	96	100	96	93	98	94	100	96	100
Required Supplemental Oxygen (Y/N)	N	N	N	N	N	N	N	N	N	N
Temperature >37.5ºC, n (%, 95%CI)	38.1	35.2	36.5	38	36.9	37	39.7	38.3	38.1	36.3
Chest Radiograph	CVCX0	CVCX0	ND	CVCX0	CVCX0	CVCX0	CVCX0	ND	CVCX0	CVCX0
CRP (mg/L)	9.5	2.6	2.6	4	0.7	57.1	16.4	0.9	5.1	68.5
Lymphocyte Count (x10^9/l)	0.5	1.4	2.2	1.1	3	0.7	2.2	1.2	0.5	0.7
Neutrophil Count (x10^9/l)	8.8	9.5	6.5	2.9	2.5	1.9	6.7	2.7	4.6	1.6
Isolated (Y / N)	N	N	N	Y	N	N	N	Y	Y	N
ICU Admission (Y / N)	N	N	N	N	N	N	N	N	N	N
Died (Y / N)	N	N	N	N	N	N	N	N	N	N
Length of stay (days)	2	1	1	1	7	2	4	2	4	1

Supplementary Table 3 footnotes: *Age on arrival is presented in terms of Decade of Life (eg. 5 = age 40 to 49 years). Imaging reports were coded as per BSTI guidelines. Chest Radiograph reports were coded as: CVCX0 = Normal; CVCX1 = Classic; CVCX2 = Indeterminate; CVCX3 = Non-COVID-19, NEWS=National Early Warning Score, SpO2=Oxygen Saturations, CRP=C-Reactive Protein, Y=Yes, N=No, ND=Not Done

Supplementary Table 5: Number of patients allocated to isolation rooms or COVID-19 cohorts in SARS-CoV-2 RT-PCR positive patients, and those requiring isolation following triage.

	SARS-CoV-2 RT-PCR Positive (n=136)	Triage Positive (n=574)	Likely (n=175)	Possible, FebriDx Positive (n=132)	Possible, FebriDx Not Done (n=267)
'Non-COVID' Area	7	68	5	4	58
Side Room	112	477	152	122	203
COVID-19 Cohort Ward	17	29	18	6	6
% Isolated	94.9	88.2	97.1	97.0	78.3

Table 5 footnotes: Actual patient movement from the emergency department extracted from the hospital's bed management system.

STARD 2015

AIM

STARD stands for "Standards for Reporting Diagnostic accuracy studies". This list of items was developed to contribute to the completeness and transparency of reporting of diagnostic accuracy studies. Authors can use the list to write informative study reports. Editors and peer-reviewers can use it to evaluate whether the information has been included in manuscripts submitted for publication.

EXPLANATION

A **diagnostic accuracy study** evaluates the ability of one or more medical tests to correctly classify study participants as having a **target condition.** This can be a disease, a disease stage, response or benefit from therapy, or an event or condition in the future. A medical test can be an imaging procedure, a laboratory test, elements from history and physical examination, a combination of these, or any other method for collecting information about the current health status of a patient.

The test whose accuracy is evaluated is called **index test.** A study can evaluate the accuracy of one or more index tests. Evaluating the ability of a medical test to correctly classify patients is typically done by comparing the distribution of the index test results with those of the **reference standard**. The reference standard is the best available method for establishing the presence or absence of the target condition. An accuracy study can rely on one or more reference standards.

If test results are categorized as either positive or negative, the cross tabulation of the index test results against those of the reference standard can be used to estimate the **sensitivity** of the index test (the proportion of participants *with* the target condition who have a positive index test), and its **specificity** (the proportion *without* the target condition who have a negative index test). From this cross tabulation (sometimes referred to as the contingency or "2x2" table), several other accuracy statistics can be estimated, such as the positive and negative **predictive values** of the test. Confidence intervals around estimates of accuracy can then be calculated to quantify the statistical **precision** of the measurements.

If the index test results can take more than two values, categorization of test results as positive or negative requires a **test positivity cut-off**. When multiple such cut-offs can be defined, authors can report a receiver operating characteristic (ROC) curve which graphically represents the combination of sensitivity and specificity for each possible test positivity cut-off. The **area under the ROC curve** informs in a single numerical value about the overall diagnostic accuracy of the index test.

The **intended use** of a medical test can be diagnosis, screening, staging, monitoring, surveillance, prediction or prognosis. The **clinical role** of a test explains its position relative to existing tests in the clinical pathway. A replacement test, for example, replaces an existing test. A triage test is used before an existing test; an add-on test is used after an existing test.

Besides diagnostic accuracy, several other outcomes and statistics may be relevant in the evaluation of medical tests. Medical tests can also be used to classify patients for purposes other than diagnosis, such as staging or prognosis. The STARD list was not explicitly developed for these other outcomes, statistics, and study types, although most STARD items would still apply.

DEVELOPMENT

This STARD list was released in 2015. The 30 items were identified by an international expert group of methodologists, researchers, and editors. The guiding principle in the development of STARD was to select

items that, when reported, would help readers to judge the potential for bias in the study, to appraise the applicability of the study findings and the validity of conclusions and recommendations. The list represents an update of the first version, which was published in 2003.

More information can be found on http://www.equator-network.org/reporting-guidelines/stard.

Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT			**1**
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	1
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	2
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	4
	4	Study objectives and hypotheses	5
METHODS			
Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	5
Participants	**6**	Eligibility criteria	5, table 1 (page 12)
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	5
	8	Where and when potentially eligible participants were identified (setting, location and dates)	5
	9	Whether participants formed a consecutive, random or convenience series	5
Test methods	**10a**	Index test, in sufficient detail to allow replication	6
	10b	Reference standard, in sufficient detail to allow replication	6
	11	Rationale for choosing the reference standard (if alternatives exist)	NA
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	5
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	NA
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	6
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	6
Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy	7
	15	How indeterminate index test or reference standard results were handled	7
	16	How missing data on the index test and reference standard were handled	7
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	NA
	18	Intended sample size and how it was determined	7
RESULTS			
Participants	**19**	Flow of participants, using a diagram	Figure 1 (page 17)
	20	Baseline demographic and clinical characteristics of participants	Table 2 (page 18)

	21a	Distribution of severity of disease in those with the target condition	Table 2 (page 18)
	21b	Distribution of alternative diagnoses in those without the target condition	NA
	22	Time interval and any clinical interventions between index test and reference standard	6
Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	Table 3 (page 20) and Supplementary Table 4
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	Table 3 (page 20)
	25	Any adverse events from performing the index test or the reference standard	NA
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	11
	27	Implications for practice, including the intended use and clinical role of the index test	12
OTHER INFORMATION			
	28	Registration number and name of registry	NA
	29	Where the full study protocol can be accessed	NA
	30	Sources of funding and other support; role of funders	12

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5 and Table 1
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	7
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Figure 1
		(b) Give reasons for non-participation at each stage	Figure 1
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 2

		(b) Indicate number of participants with missing data for each variable of interest	Table 2
		(c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	9

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	8 Table 2 NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Supplementary table 3
Discussion			
Key results	18	Summarise key results with reference to study objectives	Table 3
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Utility of the FebriDx point-of-care assay in supporting a triage algorithm for medical admissions with possible COVID-19: an observational cohort study

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Title:

Utility of the FebriDx point-of-care assay in supporting a triage algorithm for medical admissions with possible COVID-19: an observational cohort study

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ABSTRACT

Objective: To evaluate a triage algorithm used to identify and isolate patients with suspected COVID-19 among medical patients needing admission to hospital using simple clinical criteria and the FebriDx assay.

Design: Retrospective observational cohort

Setting: Large acute NHS hospital in London, UK

Participants: All medical admissions from the emergency department between 10th August 2020 and 4th November 2020 with a valid SARS-CoV-2 RT-PCR result.

Interventions: Medical admissions were triaged as likely, possible or unlikely COVID-19 based on clinical criteria. Patients triaged as possible COVID-19 underwent FebriDx lateral flow assay on capillary blood, and those positive for MxA were managed as likely COVID-19.

Primary Outcome measures: Diagnostic accuracy (sensitivity, specificity and predictive values) of the algorithm and the FebriDx assay compared to SARS-CoV-2 RT-PCR from nasopharyngeal swabs as the reference standard.

Results: 4.0% (136) of 3,443 medical admissions had RT-PCR confirmed COVID-19. Prevalence of COVID-19 was 46% (80/175) in those triaged as likely, 4.1% (50/1,225) in possible and 0.3% (6/2,033) in unlikely COVID-19. Compared to SARS-CoV-2 RT-PCR, clinical triage had sensitivity of 96% (95%CI: 91% - 98%) and specificity of 61.5% (95%CI: 59.8% - 63.1%), whilst the triage algorithm including FebriDx had sensitivity of 93% (95%CI: 87% - 96%) and specificity of 86.4% (95%CI: 85.2% - 87.5%). Whilst 2,033 patients were deemed not to require isolation using clinical criteria alone, the addition of FebriDx to clinical triage deisolated a further 826 patients from isolation, reducing the need for isolation rooms by 9.5 per day, 95%CI: 8.9 – 10.2. Ten patients missed by the algorithm had mild or asymptomatic COVID-19.

Conclusions: A triage algorithm including the FebriDx assay had good sensitivity and was useful to 'rule-out' COVID-19 among medical admissions to hospital.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Strengths
  - This was a pragmatic study of a large cohort of consecutive medical admissions enabling a real-world evaluation of the utility of the FebriDx point-of-care assay for COVID-19 triage - a novel application.
  - The analyses performed, including estimates of the number of isolation rooms saved and time-to-test result, can inform hospital management when assessing the effectiveness of the FebriDx point-of-care assay for COVID-19 triage in other settings.

- Limitations
  - A single SARS-CoV-2 RT-PCR is an imperfect reference standard for COVID-19 which may impact specificity, and multiple PCR assays were used each with their own performance characteristics.
  - The performance of the triage algorithm and the FebriDx assay may differ when used in other populations depending on the underlying prevalence of COVID-19 or other respiratory pathogens.

INTRODUCTION

The Coronavirus disease (COVID-19) pandemic, caused by SARS-CoV-2, presents unprecedented challenges for infection prevention and control (IPC) within healthcare facilities worldwide.[1] Transmission may occur via respiratory droplet, fomite, or airborne routes (following aerosol-generating procedures).[2-4] Prolonged indoor contact increases transmission, and nosocomial transmission is common.[5,6] Respiratory isolation capacity (neutral or negative pressure side-rooms) is easily saturated within healthcare facilities.[1] Decisions to isolate patients in need of admission with suspected or possible COVID-19 must be rapid and accurate to maintain patient flow from emergency departments (EDs), yet minimise risk of nosocomial transmission.

As COVID-19 can present with non-specific symptoms, diagnostic confirmation is often sought by detection of SARS-CoV-2 ribonucleic acid (RNA) by reverse transcription-polymerase chain reaction (RT-PCR) from nasopharyngeal swab (NPS).[7] However, decisions about patient isolation from the ED are usually required before the results of RT-PCR assays are available.[8,9] Even near-patient, rapid RT-PCR platforms with assay run times of 1-2 hours can be quickly overwhelmed, especially during peaks of COVID-19 incidence.[10,11] Multivariable diagnostic risk models, including clinical criteria and thoracic imaging, are not sufficient, but may be useful as a triage test to ration expensive or scarce point-of care assays.[12,13]

FebriDx (Lumos diagnostics, Sarasota, Florida, US) is a lateral flow assay that detects two host response proteins, Myxovirus resistance protein A (MxA, positive if >40ng/mL) and C-reactive protein (CRP, positive if >20mg/L) in capillary blood samples. MxA is an interferon-induced antiviral host response protein that has been studied as a biomarker to differentiate bacterial and viral respiratory infections.[14–17] More recently FebriDx has demonstrated a sensitivity of 93% and specificity of 86% for detecting COVID-19 compared to RT-PCR in hospital inpatients including patients with clinically likely COVID-19 and those without symptoms of COVID-19.[18] FebriDx could be

useful as an early triage tool to identify patients with COVID-19 and help guide isolation and IPC in patients needing admission to hospital.[18–21] We therefore developed and implemented a COVID-19 triage algorithm, supported by FebriDx, to inform patient flow from the ED whilst awaiting RT-PCR results. Here we describe the diagnostic performance of this algorithm compared to SARS-CoV-2 RT-PCR. We also describe the impact on isolation room demand and the time to FebriDx and RT-PCR results.

METHODS

Patient cohort

We utilised data prospectively entered into a COVID-19 triage database and retrospective extraction of clinical and bed allocation data from electronic patient records and hospital IT systems at Northwick Park Hospital, a large district general hospital serving a diverse population in North-West London. Patients were included if they required admission to a medical ward from the ED between 10th August 2020 and 4th November 2020 inclusive and had a valid SARS-CoV-2 RT-PCR result on admission.

Triage Algorithm

On initial assessment in the ED, consecutive medical admissions were categorised by the attending clinician into three categories for their likelihood of COVID-19 (unlikely, possible and likely), using clinical criteria such as clinical history, observations and plain chest radiograph based on Public Health England guidance (Table 1 and Supplementary Table 1).[22] Patients discharged home or admitted under specialties other than medicine and those under sixteen years of age were not triaged using the algorithm and did not receive FebriDx testing, therefore their exclusion is unlikely to be a source of ascertainment bias. Patients with epidemiological risk factors for COVID-19 (eg. recent contact with a COVID-19 case or travel to a high-risk country) were triaged as likely COVID-19. We refer to this stage of the triage algorithm as ‘clinical criteria’.

We evaluated the impact of using FebriDx in a test-to-deisolate strategy amongst patients designated as possibly having COVID-19 after clinical criteria had been applied at initial assessment. Patients in the possible group underwent testing with FebriDx unless they declined or met an exclusion criterion. Patients were excluded from FebriDx testing if they were immunosuppressed or had had symptoms of COVID-19 for more than 10 days (in these situations a measurable Type I or Type III interferon response might not be present in infected individuals, as per manufacturer's guidance). Patients were also excluded if they had a previous diagnosis of COVID-19 (self-reported or confirmed) or required high dependency unit or intensive care unit (HDU/ICU) admission due to the greater infection control consequences of incorrect triage. All patients underwent NPS testing with SARS-CoV-2 RT-PCR, with rapid RT-PCR assays being prioritised for patients in the likely group.

Only patients with confirmed COVID-19 on SARS-CoV-2 RT-PCR were admitted to a COVID-19 cohort area ('COVID ward'). Those triaged as likely, and those triaged as possible with a positive FebriDx or excluded from having a FebriDx test were designated 'Triage Positive' and admitted to an isolation room until PCR results were available. Patients assigned to the unlikely COVID-19 group and those with a negative FebriDx test were designated 'Triage Negative' and admitted to 'non-COVID wards' whilst awaiting SARS-CoV-2 RT-PCR results (Table 1 and Figure 1).

Ethics Approval

FebriDx testing was implemented as part of routine clinical care in response to data on assay performance for COVID-19 and an urgent clinical need.[21] The study was approved by the London North West University Hospitals Trust Research and Development Committee (SE20/069), and given this was a retrospective review using routinely collected clinical data, they deemed formal ethical approval was not required. Results are reported in compliance with STARD and STROBE guidelines

(see supplementary materials). The FebriDx tests were purchased independently from a UK distributer, and the manufacturer had no role in the study conception, design, data analysis or manuscript preparation.

Testing procedures and definitions

The FebriDx assay was performed as per the manufacturer's instructions at the point-of-care by trained ED health-care assistants. In brief, 5µL of capillary blood is placed on the sample window and reagents are released by pressing a button. The result is read after 10 minutes, with a positive result being the presence of a blue line in the control window and a red line in the MxA window (limit of detection 40ng/ml). The results from the CRP window were not used given all patients had laboratory CRP measurements. Staff performing FebriDx had access to clinical information but not SARS CoV-2 RT-PCR results at the time of FebriDx testing. Routine SARS CoV-2 RT-PCR was done on NPS using either the Panther Fusion SARS-CoV-2 (Hologic Inc, CA, USA), Abbott RealTime SARS-CoV-2 (Abbott Park, IL, USA) or an extraction-free SARS-CoV-2 RT-PCR assay developed by Health Services Laboratories (HSL), UK.[23] Rapid RT-PCR assays used were Xpert Xpress SARS-CoV-2 (Cepheid, CA, USA) or SAMBA II SARS-CoV-2 (Diagnostics for the Real World, CA, USA).

Patients were defined as having COVID-19 or not based on the first valid RT-PCR result up to 72 hours after admission. Patients without a valid RT-PCR result or triage status were excluded from the analysis. Vital signs, including National Early Warning Score (NEWS) were recorded on arrival to the ED. All biochemical, haematological and radiological data were from the first results within 48 hours of admission. Thoracic imaging (chest radiographs and CT) were reported and coded based upon guidelines on COVID-19 from the British Society of Thoracic Imaging (BSTI) at the time of reporting by radiologists.[24] Vital status is reported at the time of hospital discharge or data extraction (20th November 2020) for those who were still inpatients.

Data Analysis and Statistical Methods

We evaluated the real-world diagnostic performance (sensitivity, specificity, and positive and negative predictive values with 95% confidence intervals) of the triage algorithm (described above and in Figure 1) using both clinical criteria (described above and in Table 1) and the FebriDx assay in combination compared to a SARS-CoV-2 RT-PCR from a single NPS reference standard. We also evaluated each stage of the triage algorithm independently, estimating measures of diagnostic performance for triage using clinical criteria alone and the FebriDx assay in patients with possible COVID-19 compared to a SARS-CoV-2 RT-PCR reference standard. Patients with missing RT-PCR or those missing data on triaging were excluded from analysis. We also reported the time from arrival to FebriDx and RT-PCR results. We described the proportion of patients with COVID-19 who were correctly isolated, estimated the number of isolation beds made available by FebriDx testing, and described the patients with COVID-19 who were incorrectly triaged by the algorithm. Basic descriptive statistics were performed, with comparisons made using chi-squared tests for proportions, t-tests for means and Wilcoxon rank sum to compare non-normally distributed populations. Logistic regression was used to compare age and sex adjusted estimates of in-hospital death in each triage group, using complete cases only. Statistical analyses were performed using Stata version 14.0 (StataCorp, LLC, College Station TX). Based on an anticipated sensitivity of 93%, a sample size of 3335 would estimate the sensitivity of the triage algorithm ±5% with alpha 0.05 and prevalence of 3%.

Patient and Public Involvement

There was no patient involvement in the development of the research question, study design or conduct of the study.

RESULTS

Baseline characteristics and COVID-19 diagnosis

Between the 10th August and 4th November 2020, there were 9,645 emergency department visits resulting in further hospital care. Of these, 3,433 (35.6%) were adult medical patients admitted for further treatment, were triaged using the algorithm based on COVID-19 status and had a valid SARS-CoV-2 RT-PCR result (figure 1). 175 (5.1%) patients were triaged as likely COVID-19, 2,033 (59.2%) patients as unlikely COVID-19 and 1,225 (35.7%) patients were triaged into the possible COVID-19 category. Key patient characteristics are given in Table 2.

There were several differences between the three triage groups (Table 2). The likely COVID-19 group were younger, had higher NEWS scores on arrival and more frequently required supplemental oxygen compared to the unlikely group and the possible group ($p<0.02$ for all comparisons). As expected, more patients in the likely COVID-19 group had chest radiograph changes typical for COVID-19 than in the possible ($p<0.001$), and the unlikely COVID-19 group ($p<0.001$). The possible COVID-19 group were older than the other two groups and were more likely to have an elevated neutrophil count than the likely or possible groups.

Overall, 136/3,443 admissions (4.0%) were diagnosed with PCR-confirmed COVID-19. Prevalence of COVID-19 was 46% (80/175) in likely patients, and 4.1% (50/1,225) in the possible group. Of those triaged as unlikely COVID-19, only 6/2,033 (0.3%) were SARS-CoV-2 RT-PCR positive.

Performance of FebriDx and triage algorithm

The overall diagnostic performance of the clinical triage algorithm compared to the gold standard of SARS-CoV-2 RT-PCR is summarised in table 3. 958 (78.2%) patients in the possible group were tested using FebriDx (those excluded are detailed in figure 1). 13.8% (132/958) of FebriDx test results were positive for MxA, with 86.2% negative and no invalid results. The median duration of COVID-19

symptoms in patients tested by FebriDx was 2 days (IQR 1-3, n=847). Patients with positive FebriDx results were younger, more likely to be febrile and less likely to have raised neutrophil counts than FebriDx negative patients (supplementary table 2).

31% (41/132) of patients with a positive FebriDx had a positive SARS-CoV-2 RT-PCR, whilst only 4/826 (0.5%) with a negative FebriDx were diagnosed as having COVID-19. All 4 patients with false-negative FebriDx results had normal chest radiographs. 2 patients tested negative for COVID-19 by SARS-CoV-2 RT-PCR but had positive FebriDx results and chest radiograph appearances typical for COVID-19. In the possible COVID-19 group, FebriDx results were available a median of 2.2 hours (IQR: 1.4 to 3.1, n=808) and RT-PCR results a median of 17.8 hours (IQR: 11.35 – 25.34, n=456) after arrival to the ED (figure 2). 88.0% of FebriDx results were available within 4 hours of arrival (n=808).

The triage algorithm correctly identified 126/136 patients with PCR-confirmed COVID-19 in the likely group (sensitivity 93%, 95%CI: 87 - 96) (table 3). The 10 patients who were SARS-CoV-2 RT-PCR positive but missed by the triage algorithm are described in supplementary table 3. 6/10 were classified as unlikely, and 4/10 were classified as possible COVID-19 and had a negative FebriDx. 2/10 were febrile on admission, none required supplemental oxygen, length of stay was short (median 2 days) and 8 had normal chest radiographs (2 did not have thoracic imaging done). Specificity of the algorithm was 86.4% (85.2 - 87.5), and negative predictive value was 99.7% (99.4 - 99.8).

Outcomes

95% (129/136) of patients with COVID-19 were appropriately managed in isolation rooms or COVID cohort wards as a result of the triage algorithm (supplementary table 4). Of the 10 patients with PCR-confirmed COVID-19 not identified by the triage algorithm, 7 were initially managed in a non-COVID ward. Had all patients been isolated until SARS-CoV-2 RT-PCR result was available (ie without using clinical criteria or FebriDx to de-isolate) 2,859 more isolation rooms would have been used.

When using the triage algorithm, clinical criteria allowed 2,033 patients to be deisolated from isolation after being classified as unlikely COVID-19. The addition of FebriDx to clinical triage allowed 826 more patients to be managed in 'non-COVID' wards than if all patients triaged possible COVID-19 had required isolation (9.5 isolation rooms saved per day, 95%CI: 8.9 – 10.2).

11 (8%) patients with COVID-19 died compared to 150 (4.5%) without COVID-19 (p=0.042). Age and sex adjusted odds of death during the admission were higher for patients in the likely (OR: 3.42, 95% CI: 1.81 - 6.45) and possible groups (OR: 2.44, 95% CI: 1.73 - 3.44) than the unlikely COVID-19 group.

DISCUSSION

Our main findings are that a pragmatic triage algorithm using simple clinical parameters available within the ED and the FebriDx point-of-care test had good sensitivity (93%) and excellent NPV (99.7%) for COVID-19 diagnosed by RT-PCR. Inclusion of FebriDx improved the specificity of triage with minimal reductions in sensitivity, allowing a substantial reduction in the number of isolation rooms needed.

Although clinicians were able to identify patients likely and unlikely to have COVID-19 (46% and 0.3% of whom had confirmed COVID-19 respectively) based on clinical assessment, radiology and basic blood tests, their assessment was not sufficiently specific. Patients identified as 'possible' COVID-19 still had a 4% prevalence of COVID-19, and were a large enough group to overwhelm isolation room capacity. We demonstrate a simple, rapid test performed at the point-of-care can help further risk stratify this group. In real-life settings in a busy ED, a point-of-care test was able to inform isolation decisions within 4 hours of arrival compared to PCR results which were too slow to inform patient flow from ED, even when using 'rapid' PCR assays. Although formal cost-effectiveness analysis was not performed, each FebriDx test only costs about US$18, and this may lead to cost savings.

The strengths of this study are its pragmatic design under routine clinical settings, and that we are able to account for over 95% of medical admissions, reducing risks of bias. There are, however, several limitations. A single SARS-CoV-2 RT-PCR is an imperfect reference standard, and does not account for RT-PCR negative COVID-19 patients. We used multiple RT-PCR platforms, which will have different PCR targets and performance. 10% of patients in the possible group did not get tested with FebriDx for unclear reasons, which could be a source of bias unless these were unavoidable random losses in a busy ED department. The prevalence of COVID-19 was 4.0% in this cohort, and it is unclear what impact a higher prevalence of COVID-19 or other respiratory pathogens such as

influenza would have on these findings. The criteria for likely and possible COVID-19 groups changed subtly during the study period, although this is unlikely to significantly alter the outcomes.

These data build on previous studies of FebriDx showing good sensitivity, and utility as a 'rule-out' test for COVID-19.[17–20] The estimate of sensitivity of FebriDx for detecting COVID-19 in our cohort is lower than previously described, likely because our testing strategy differs in that it does not include patients deemed likely to have COVID-19 by clinical criteria. Testing this group would have been unlikely to alter clinical decisions, even if FebriDx had been negative, given the high pre-test probability. The FebriDx test allowed patients with possible COVID-19 to be divided into two groups with similar characteristics and clinical features, but vastly different COVID-19 prevalence (0.5% in FebriDx negative, and 31% in FebriDx positive). However, about 10% of patients in this group were not eligible for FebriDx testing, and had to be managed in isolation rooms as triage-positive patients (see Figure 1).

Only ten patients with COVID-19 were incorrectly triaged by the algorithm, four of whom were tested and 'missed' using FebriDx. These patients were younger, less symptomatic, did not have chest radiograph changes, and mostly likely had mild or asymptomatic COVID-19 infection. Given that MxA is an intracellular GTPase induced by type I and type III interferon responses, it is plausible that sensitivity would be lower in oligo- or asymptomatic infection.[25] Although the patients missed by the algorithm are potential sources of nosocomial transmission, asymptomatic disease is thought to be less transmissible.[26] We found no nosocomial cases related to these patients.

In conclusion, we demonstrate a simple triage system including the novel FebriDx point-of-care test had good sensitivity and negative predictive value for COVID-19 and utility for managing medical admissions from the ED.

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Author contributions

HH, AGW, LJ, SF, JBL, JR, N Vaughan, N Vaid, GGR, and AKA made substantial contribution to the conception of the work. HH, AGW, LJ, and GD made substantial contribution to the design of the work. HH, GD, SN, KS, SP, MGD, and MT contributed to data acquisition. HH and AGW analysed the data. HH, AGW and LJ contributed to data interpretation. HH and AGW drafted the manuscript. All authors contributed to revising the manuscript critically for important intellectual content, approved the final manuscript and are accountable for all aspects of the work.

Competing interests statement

The authors have no competing interests to declare.

Data availability statement

Data are available upon reasonable request, subject to approval by the London North West University Healthcare NHS Trust Research and Governance Department and approval from relevant ethics and regulatory bodies.

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Tables

COVID-19 triage category	Clinical Criteria	Diagnostics performed in ED	Bed Allocation from ED
Likely	Recent Contact with a confirmed COVID-19 case OR Travel to High Risk country within the last 14 days	Routine RT-PCR	Isolation Room
	Known COVID-19 illness confirmed within the last 14 days prior to current attendance	Urgent RT-PCR	COVID-19 cohort ward or isolation room
	High Clinical Suspicion (eg. Oxygen Requirement, Bilateral infiltrates, Normal WCC/high CRP) OR Change in Normal sense of Smell or Taste		Isolation Room
Possible	Clinical or Radiological Pneumonia OR Fever / Persistent Cough / Shortness of Breath / Hypoxia / Diarrhoea / Confusion	FebriDx * & Urgent RT-PCR	**FebriDx Positive (or not done) → Isolation Room**
			FebriDx Negative → Non-COVID ward
Unlikely	None of the Above	Routine RT-PCR	Non-COVID ward

Table 1. Clinical Criteria for determining triage groups, testing strategy and bed allocation from the Emergency Department prior to RT-PCR result. Clinical criteria for determining triage groups are shown as of 08/10/2020. Changes to these criteria over time are detailed in supplementary table 1. * Patients were excluded from FebriDx testing if they had a prior history of COVID-19, were immunosuppressed, required intensive care or high dependency unit admission, or had had COVID-19 symptoms for > 10 days. RT-PCR=Reverse transcription polymerase chain reaction, ED=Emergency department

Variable	Unlikely	Possible	Likely
N	2033	1225	175
Age (years) median (IQR)	69 (49, 82)	75 (60, 84)	62 (48, 74)
Age over 65 years, n (%, 95%CI)	1128 (55.5%, 53.3; 57.6)	846 (69.1%, 66.5; 71.6)	79 (45%, 38; 53)
Female Sex, n (%, 95%CI)	969 (47.7%, 45.5; 49.8)	603 (49.2%, 46.4; 52.0)	72 (41%, 34; 48)
Male Sex, n (%, 95%CI)	1064 (52.3%, 50.2; 54.5)	622 (50.8%, 48.0; 53.6)	103 (59%, 52; 66)
NEWS, median (IQR)	1 (0, 3)	4 (2, 6)	5 (3, 7)
Respiratory Rate (breaths/min), median (IQR)	18 (18, 20)	24 (20, 28)	24 (21, 32)
SpO2 <94%, n (%, 95%CI)	61 (3.1%, 2.4; 3.9)	234 (19.5%, 17.3; 21.8)	38 (22%, 17; 29)
Required Supplemental Oxygen, n (%, 95%CI)	52 (2.7%, 2.0; 3.4)	245 (20.4%, 18.1; 22.7)	52 (30%, 24; 38)
Temperature >37.5ºC, n (%, 95%CI)	172 (8.8%, 7.6; 10.1)	359 (30.0%, 27.4; 32.6)	73 (43%, 35; 50)
Chest Radiograph - Normal, n (%, 95%CI)	1171 (81.0%, 79.0; 83.0)	537 (49.9%, 46.9; 52.9)	42 (30%, 22; 37)
Chest Radiograph - Typical for COVID-19, n (%, 95%CI)	4 (0.3%, 0.0; 0.5)	25 (2.3%, 1.4; 3.2)	54 (38%, 30; 46)
Chest Radiograph - Other, n (%, 95%CI)	271 (18.7%, 16.7; 20.8)	514 (47.8%, 44.8; 50.8)	45 (32%, 24; 40)
Chest CT - Normal, n (%, 95%CI)	8 (24%, 12; 41)	9 (16%, 9; 29)	0 (0%, 0; 0)
Chest CT - Typical for COVID-19, n (%, 95%CI)	0 (0%, 0; 0)	3 (5%, 2; 16)	3 (43%, 10; 83)
Chest CT - Other, n (%, 95%CI)	26 (76%, 59; 88)	43 (78%, 65; 87)	4 (57%, 17; 90)
CRP (mg/L), median (IQR)	5.7 (1.4, 26.9)	26.4 (7.05, 87.65)	53.7 (25.9, 122.7)
CRP >20mg/L, n (%, 95%CI)	545 (28.7%, 26.7; 30.7)	656 (55.8%, 52.9; 58.6)	134 (80%, 74; 86)
Lymphocyte Count <1.0x10^9/l, n (%, 95%CI)	373 (25.3%, 23.1; 27.5)	383 (43.9%, 40.6; 47.2)	70 (55%, 46; 63)
Neutrophil Count >7.5x10^9/l, n (%, 95%CI)	620 (32.0%, 29.9; 34.0)	598 (50.4%, 47.6; 53.3)	61 (36%, 29; 43)
Crude In Hospital Mortality, n (%, 95%CI)	57 (2.8%, 2.1; 3.6)	89 (7.5%, 6.0; 9.0)	13 (8%, 4; 12)
SARS-CoV-2 RNA Detectable on RT-PCR, n (%, 95%CI)	6 (0.3%, 0.1; 0.5)	50 (4.1%, 3.0; 5.2)	80 (46%, 38; 53)

Table 2: Baseline characteristics, vital signs, initial investigations, mortality and SARS-CoV-2 RT-PCR results for patients in the unlikely, possible and likely COVID-19 groups. For observations on arrival, 3.2 to 4.1% of data were missing. Data were missing for 5.5% of CRP results and 4.0% of haematology results, 22.4% of chest radiograph reports and 2.1% of vital status. 96 patients (2.8%) had a chest CT report available. Imaging reports were coded as per BSTI guidelines. Chest Radiograph reports were coded as: CVCX0 = Normal; CVCX1 = Typical; CVCX2 = Indeterminate; CVCX3 = Non-COVID-19. Chest CT

reports were coded as: CVCT0= Normal; CVCT1= Typical; CVCT2= Indeterminate; CVCT3= Non-COVID-19. IQR=Inter-quartile range, CI=Confidence Interval, NEWS=National Early Warning Score, SpO2=Oxygen Saturations, CRP=C-Reactive Protein, CT=Computerised Tomography

A		SARS-CoV-2 RT-PCR			
		Positive	Negative	Total	
Clinical criteria alone (without FebriDx) (n=3433)	Likely or Possible COVID-19	130	1270	1400	PPV: 9.3% (95% CI: 7.9 – 10.9)
	Unlikely COVID-19	6	2027	2033	NPV: 99.7% (95% CI: 99.3 – 99.9)
	Total	136	3297	3433	
		Sensitivity 96% (95% CI: 91 – 98)	Specificity 61.5% (95% CI: 59.8 – 63.1)		

B		SARS-CoV-2 RT-PCR			
		Positive	Negative	Total	
FebriDx alone in the possible COVID-19 group with FebriDx done. (n=958)	FebriDx Positive	41	91	132	PPV: 31% (95% CI: 24 – 39)
	FebriDx Negative	4	822	826	NPV: 99.5% (95% CI: 98.7 – 99.8)
	Total	45	913	958	
		Sensitivity 91% (95% CI: 78 – 97)	Specificity 90.0% (95% CI: 87.9 – 91.8)		

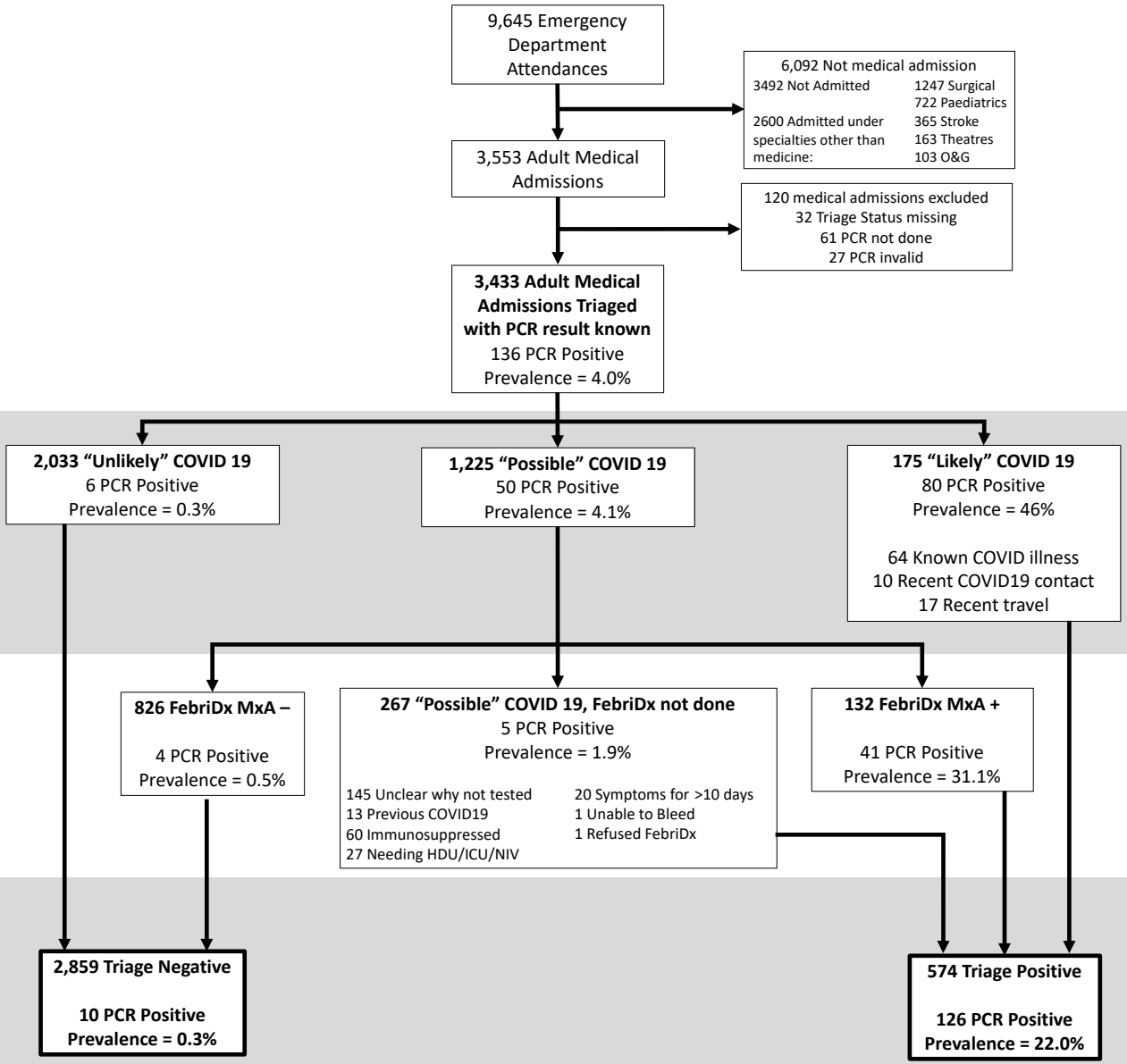
C		SARS-CoV-2 RT-PCR			
		Positive	Negative	Total	
Triage Algorithm using clinical criteria and FebriDx (n=3433)	Triage Positive	126	448	574	PPV: 22% (95% CI: 19 - 26)
	Triage Negative	10	2849	2859	NPV: 99.7% (95% CI: 99.4 - 99.8)
	Total	136	3297	3433	
		Sensitivity 93% (95% CI: 87 - 96)	Specificity 86.4% (95% CI: 85.2 - 87.5)		

Table 3 Cross tabulation of results of the triage algorithm with and without FebriDx as well as the results of FebriDx within the possible COVID-19 group compared to a SARS-CoV-2 RT-PCR reference standard. Measures of Diagnostic Performance are presented for the triage algorithm for the detection of COVID-19: 3A) Using clinical criteria alone without FebriDx, where subjects are classified as positive or negative based on clinical criteria shown in Table 1. Subjects were 'positive' if they were assigned as likely or possible COVID-19 based on clinical criteria alone. 3B) Using the FebriDx assay alone within the possible COVID-19 group receiving a FebriDx test. Subjects are classed as FebriDx positive or negative based on the FebriDx test only. 3C) Using clinical criteria supported by the FebriDx assa. Subjects were classed as Triage positive or negative based on their flow through the algorithm as shown in figure 1. Patients were Triage positive if they were triaged as likely COVID-19 or possible COVID-19 without a negative FebriDx result. Patients were Triage Negative if they were triaged as unlikely COVID-19 or possible COVID-19 with a negative FebriDx result. PPV = Positive Predictive Value, NPV = Negative Predictive Value, CI = Confidence Interval

Figure Legends:

Figure 1: Patient flow through the study and the COVID-19 triage algorithm
Patients were included if they required admission to a medical ward from the ED between 10th August 2020 and 4th November 2020 inclusive. Patients were excluded if they were under sixteen years of age, admitted under specialities other than medicine, or if their triage status or SARS-CoV-2 RT-PCR result was unknown. Counts at each stage of triage are shown in 2x2 tables on the right. These counts correspond with the 2x2 tables and measures of diagnostic performance shown in Table 3. PCR = SARS-CoV-2 RT-PCR.

Figure 2: Time from arrival to the availability of FebriDx and SARS-CoV-2 RT-PCR results
Kernel frequency density plot using the Epanechniko function; Time to FebriDx result was calculated as the time from arrival to the emergency department until the time the FebriDx result was recorded (blue plot), bandwidth=0.3; Time to RT-PCR result was calculated as the time from arrival to to the emergency department until the time the SARS-CoV-2 RT-PCR result was recorded (red plot), bandwidth=2.



		SARS-CoV-2 RT-PCR	
		Positive	Negative
Clinical Criteria Alone	1400 Positive (1225 possible & 175 likely)	130	1270
See Table 3A	2033 Negative (unlikely)	6	2027

		SARS-CoV-2 RT-PCR	
		Positive	Negative
FebriDx Alone	132 FebriDx Positive	41	91
See Table 3B	826 FebriDx Negative	4	822

		SARS-CoV-2 RT-PCR	
		Positive	Negative
Triage Algorithm using Clinical Criteria and FebriDx	574 Triage Positive	126	448
See Table 3C	2859 Triage Negative	10	2849

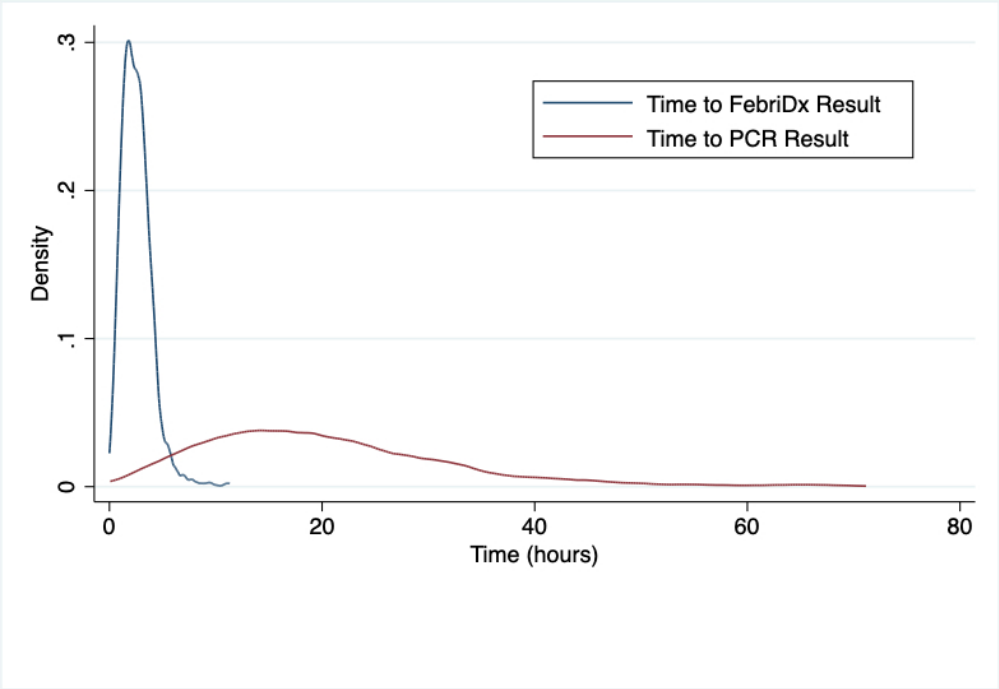


Figure 2

276x191mm (72 x 72 DPI)

Use of the FebriDx point-of-care assay as part of a triage algorithm for medical admissions with possible COVID-19

Supplementary Tables:

Supplementary Table 1: Changes made to the inclusion criteria for the triage categories and the exclusion criteria for FebriDx testing during the study period.

<table>
<tr><td></td><td colspan="4">Date of Update to COVID-19 Triage Criteria</td></tr>
<tr><td></td><td>06/07/2020</td><td>09/09/2020</td><td>21/09/2020</td><td>08/10/2020</td></tr>
<tr><td rowspan="5">Likely</td><td colspan="4">Confirmed COVID-19 during current illness</td></tr>
<tr><td colspan="4">High Clinical Suspicion
(eg. Oxygen Requirement, Bilateral infiltrates, Normal WCC/high CRP)</td></tr>
<tr><td colspan="4">Recent Contact with a confirmed COVID-19 case</td></tr>
<tr><td colspan="4">Travel to High Risk country within the last 14 days</td></tr>
<tr><td colspan="3"></td><td>Change in Normal sense of Smell or Taste</td></tr>
<tr><td rowspan="4">Possible</td><td colspan="3">Change in Normal sense of Smell or Taste</td><td></td></tr>
<tr><td colspan="4">Clinical or Radiological Pneumonia</td></tr>
<tr><td colspan="2">Fever PLUS Persistent Cough OR Shortness of Breath OR Hypoxia</td><td colspan="2">Fever OR Persistent Cough OR Shortness of Breath OR Hypoxia</td></tr>
<tr><td colspan="3"></td><td>Confusion OR Diarrhoea</td></tr>
<tr><td>Unlikely</td><td colspan="4">None of the Above</td></tr>
<tr><td rowspan="4">Exclusion Criteria for FebriDx</td><td colspan="4">Immunosuppressed</td></tr>
<tr><td colspan="4">Previous COVID-19</td></tr>
<tr><td></td><td colspan="3">Requiring ITU/HDU/NIV</td></tr>
<tr><td colspan="2"></td><td colspan="2">COVID-19 Symptoms >10 days</td></tr>
</table>

Supplementary Table 1 footnotes:
The inclusion criteria for the triage categories and the exclusion criteria for FebriDx testing were adjusted during the course of this pragmatic study. WCC=white cell count, CRP= C-Reactive Protein, ITU=Intensive Therapy Unit, HDU=High Dependency Unit, NIV=Non-Invasive ventilation.

Supplementary Table 2: Baseline characteristics, vital signs, initial investigations, mortality and SARS-CoV-2 RT-PCR results for patients in the possible COVID-19 group by FebriDx test result

Variable	FebriDx Negative	FebriDx Positive	FebriDx Not Done
N	826	132	267
Age (years) median (IQR)	77 (61, 85)	69.5 (54.5, 81.5)	72 (60, 81)
Age over 65 years, n (%, 95%CI)	586 (70.9, 67.8; 74.0)	80 (61, 52; 69)	180 (67, 62; 73)
Female Sex, n (%, 95%CI)	399 (48.3, 44.9; 51.7)	63 (48, 39; 56)	141 (53, 47; 59)
Male Sex, n (%, 95%CI)	427 (51.7, 48.3; 55.1)	69 (52, 44; 61)	126 (47, 41; 53)
NEWS, median (IQR)	4 (2, 7)	4 (3, 6)	4 (2, 6)
Respiratory Rate (breaths/min), median (IQR)	24 (20, 28)	24 (20, 28)	24 (19, 28)
SpO2 <94%, n (%, 95%CI)	164 (20.2, 17.6; 23.1)	24 (19, 13; 26)	46 (18, 14; 23)
Required Supplemental Oxygen, n (%, 95%CI)	170 (20.9, 18.2; 23.8)	21 (16, 11; 24)	54 (21, 16; 26)
Temperature >37.5ºC, n (%, 95%CI)	245 (30.2, 27.1; 33.4)	55 (43, 34; 51)	59 (23, 18; 29)
Chest Radiograph - Normal, n (%, 95%CI)	375 (51.2, 47.6; 54.9)	52 (43, 35; 52)	110 (49, 43; 56)
Chest Radiograph - Typical for COVID-19, n (%, 95%CI)	8 (1.1, 0.6; 2.2)	11 (9, 5; 16)	6 (3, 1; 6)
Chest Radiograph - Other, n (%, 95%CI)	349 (47.7, 44.1; 51.3)	57 (48, 39; 57)	108 (48, 42; 55)
Chest CT - Normal, n (%, 95%CI)	9 (20, 10; 34)	0 (0)	0 (0)
Chest CT - Typical for COVID-19, n (%, 95%CI)	2 (4, 1; 17)	0 (0)	1 (17, 1; 81)
Chest CT - Other, n (%, 95%CI)	35 (76, 61; 87)	3 (100)	5 (83, 19; 99)
CRP (mg/L), median (IQR)	26 (7, 96)	37.05 (17.1, 78.9)	18.85 (4.9, 76.3)
CRP >20mg/L, n (%, 95%CI)	443 (55.9, 52.5; 59.4)	87 (67, 58; 75)	126 (50, 43; 56)
Lymphocyte Count <1.0x10^9/l, n (%, 95%CI)	263 (43.8, 39.9; 47.8)	46 (48, 38; 58)	74 (42, 35; 49)
Neutrophil Count >7.5x10^9/l, n (%, 95%CI)	422 (52.8, 49.3; 56.3)	50 (38, 30; 47)	126 (49, 43; 55)
Mortality, n (%, 95%CI)	65 (8.1, 6.4; 10.2)	6 (5, 2; 10)	18 (7, 4; 11)
SARS-CoV2 RNA Detectable on RT-PCR, n (%, 95%CI)	4 (0.5, 0.3; 1.3)	41 (31, 24; 40)	5 (2, 1; 4)

Supplementary Table 2 footnotes: Missing data are summarised in the footnotes to table 2 in the main text. Imaging reports were coded as per BSTI guidelines. Chest Radiograph reports were coded as: CVCX0 = Normal; CVCX1 = Classic; CVCX2 = Indeterminate; CVCX3 = Non-COVID-19. Chest CT reports were coded as: CVCT0= Normal; CVCT1= Classic/probable; CVCT2= Indeterminate; CVCT3= Non-COVID-19. IQR=Inter-quartile range, CI=Confidence Interval, NEWS=National Early Warning Score, SpO2=Oxygen Saturations, CRP=C-Reactive Protein, CT=Computerised Tomography

Supplementary Table 3: Baseline characteristics of patients with positive SARS-CoV-2 RT-PCR results who were classified as triage negative by the algorithm

Case	1	2	3	4	5	6	7	8	9	10
Triage Status	Unlikely						Possible, FebriDx Negative			
Decade of Life*	5	7	3	5	7	6	6	3	7	5
Sex (F/M)	F	M	F	M	M	M	F	M	F	F
Presentation	Fever and epigastric pain	Hypoglycaemic collapse	Hyperkalaemia on clinic bloods	Herpes Zoster	Intentional Overdose	Unstable Angina	URTI symptoms	Diarrhoea	Fever and SOB	Headache and anosmia
Duration of Symptoms (days)	x	x	x	x	x	x	5	7	1	2
NEWS on Arrival	4	1	0	1	2	1	7	2	3	3
Respiratory Rate (breaths/min)	20	18	18	20	14	18	32	18	22	21
SpO2 (%)	97	96	100	96	93	98	94	100	96	100
Required Supplemental Oxygen (Y/N)	N	N	N	N	N	N	N	N	N	N
Temperature ºC	38.1	35.2	36.5	38	36.9	37	39.7	38.3	38.1	36.3
Chest Radiograph	CVCX0	CVCX0	ND	CVCX0	CVCX0	CVCX0	CVCX0	ND	CVCX0	CVCX0
CRP (mg/L)	9.5	2.6	2.6	4	0.7	57.1	16.4	0.9	5.1	68.5
Lymphocyte Count (x10^9/l)	0.5	1.4	2.2	1.1	3	0.7	2.2	1.2	0.5	0.7
Neutrophil Count (x10^9/l)	8.8	9.5	6.5	2.9	2.5	1.9	6.7	2.7	4.6	1.6
Isolated (Y / N)	N	N	N	Y	N	N	N	Y	Y	N
ICU Admission (Y / N)	N	N	N	N	N	N	N	N	N	N
Died (Y / N)	N	N	N	N	N	N	N	N	N	N
Length of stay (days)	2	1	1	1	7	2	4	2	4	1

Supplementary Table 3 footnotes: *Age on arrival is presented in terms of Decade of Life (eg. 5 = age 40 to 49 years).Duration of symptoms was recorded only for patients with a clinical syndrome compatible with COVID-19 tested by FebriDx. Observations presented are those measured on arrival to the Emergency Department. Imaging reports were coded as per BSTI guidelines. Chest Radiograph reports were coded as: CVCX0 = Normal; CVCX1 = Classic;

CVCX2 = Indeterminate; CVCX3 = Non-COVID-19, NEWS=National Early Warning Score, SpO2=Oxygen Saturations, CRP=C-Reactive Protein, Y=Yes, N=No, ND=Not Done

Supplementary Table 4: Actual bed allocation to isolation rooms or COVID-19 cohorts in SARS-CoV-2 RT-PCR positive patients, and those requiring isolation following triage.

	SARS-CoV-2 RT-PCR Positive (n=136)	Triage Positive (n=574)	Likely (n=175)	Possible, FebriDx Positive (n=132)	Possible, FebriDx Not Done (n=267)
'Non-COVID' Ward	7	68	5	4	58
Isolation Room	112	477	152	122	203
COVID-19 Cohort Ward	17	29	18	6	6
% Isolated	95	88.2	97	97	78

Table 4 footnotes: Actual patient movement from the emergency department extracted from the hospital's bed management system.

STARD 2015

AIM

STARD stands for "Standards for Reporting Diagnostic accuracy studies". This list of items was developed to contribute to the completeness and transparency of reporting of diagnostic accuracy studies. Authors can use the list to write informative study reports. Editors and peer-reviewers can use it to evaluate whether the information has been included in manuscripts submitted for publication.

EXPLANATION

A **diagnostic accuracy study** evaluates the ability of one or more medical tests to correctly classify study participants as having a **target condition.** This can be a disease, a disease stage, response or benefit from therapy, or an event or condition in the future. A medical test can be an imaging procedure, a laboratory test, elements from history and physical examination, a combination of these, or any other method for collecting information about the current health status of a patient.

The test whose accuracy is evaluated is called **index test.** A study can evaluate the accuracy of one or more index tests. Evaluating the ability of a medical test to correctly classify patients is typically done by comparing the distribution of the index test results with those of the **reference standard**. The reference standard is the best available method for establishing the presence or absence of the target condition. An accuracy study can rely on one or more reference standards.

If test results are categorized as either positive or negative, the cross tabulation of the index test results against those of the reference standard can be used to estimate the **sensitivity** of the index test (the proportion of participants *with* the target condition who have a positive index test), and its **specificity** (the proportion *without* the target condition who have a negative index test). From this cross tabulation (sometimes referred to as the contingency or "2x2" table), several other accuracy statistics can be estimated, such as the positive and negative **predictive values** of the test. Confidence intervals around estimates of accuracy can then be calculated to quantify the statistical **precision** of the measurements.

If the index test results can take more than two values, categorization of test results as positive or negative requires a **test positivity cut-off**. When multiple such cut-offs can be defined, authors can report a receiver operating characteristic (ROC) curve which graphically represents the combination of sensitivity and specificity for each possible test positivity cut-off. The **area under the ROC curve** informs in a single numerical value about the overall diagnostic accuracy of the index test.

The **intended use** of a medical test can be diagnosis, screening, staging, monitoring, surveillance, prediction or prognosis. The **clinical role** of a test explains its position relative to existing tests in the clinical pathway. A replacement test, for example, replaces an existing test. A triage test is used before an existing test; an add-on test is used after an existing test.

Besides diagnostic accuracy, several other outcomes and statistics may be relevant in the evaluation of medical tests. Medical tests can also be used to classify patients for purposes other than diagnosis, such as staging or prognosis. The STARD list was not explicitly developed for these other outcomes, statistics, and study types, although most STARD items would still apply.

DEVELOPMENT

This STARD list was released in 2015. The 30 items were identified by an international expert group of methodologists, researchers, and editors. The guiding principle in the development of STARD was to select

items that, when reported, would help readers to judge the potential for bias in the study, to appraise the applicability of the study findings and the validity of conclusions and recommendations. The list represents an update of the first version, which was published in 2003.

More information can be found on http://www.equator-network.org/reporting-guidelines/stard.

Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT			**1**
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	1
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	2
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	4
	4	Study objectives and hypotheses	5
METHODS			
Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	5
Participants	**6**	Eligibility criteria	5, table 1 (page 12)
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	5
	8	Where and when potentially eligible participants were identified (setting, location and dates)	5
	9	Whether participants formed a consecutive, random or convenience series	5
Test methods	**10a**	Index test, in sufficient detail to allow replication	6
	10b	Reference standard, in sufficient detail to allow replication	6
	11	Rationale for choosing the reference standard (if alternatives exist)	NA
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	5
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	NA
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	6
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	6
Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy	7
	15	How indeterminate index test or reference standard results were handled	7
	16	How missing data on the index test and reference standard were handled	7
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	NA
	18	Intended sample size and how it was determined	7
RESULTS			
Participants	**19**	Flow of participants, using a diagram	Figure 1 (page 17)
	20	Baseline demographic and clinical characteristics of participants	Table 2 (page 18)

	21a	Distribution of severity of disease in those with the target condition	Table 2 (page 18)
	21b	Distribution of alternative diagnoses in those without the target condition	NA
	22	Time interval and any clinical interventions between index test and reference standard	6
Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	Table 3 (page 20) and Supplementary Table 4
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	Table 3 (page 20)
	25	Any adverse events from performing the index test or the reference standard	NA
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	11
	27	Implications for practice, including the intended use and clinical role of the index test	12
OTHER INFORMATION			
	28	Registration number and name of registry	NA
	29	Where the full study protocol can be accessed	NA
	30	Sources of funding and other support; role of funders	12

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5 and Table 1
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	7
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Figure 1
		(b) Give reasons for non-participation at each stage	Figure 1
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 2

		(b) Indicate number of participants with missing data for each variable of interest	Table 2
		(c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	9

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	8 Table 2 NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Supplementary table 3
Discussion			
Key results	18	Summarise key results with reference to study objectives	Table 3
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

Utility of the FebriDx point-of-care assay in supporting a triage algorithm for medical admissions with possible COVID-19: an observational cohort study

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BMJ Open: Original Research Article

Title:

Utility of the FebriDx point-of-care assay in supporting a triage algorithm for medical admissions with possible COVID-19: an observational cohort study

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Running Title: FebriDx triage for COVID-19

ABSTRACT

Objective: To evaluate a triage algorithm used to identify and isolate patients with suspected COVID-19 among medical patients needing admission to hospital using simple clinical criteria and the FebriDx assay.

Design: Retrospective observational cohort

Setting: Large acute NHS hospital in London, UK

Participants: All medical admissions from the emergency department between 10th August 2020 and 4th November 2020 with a valid SARS-CoV-2 RT-PCR result.

Interventions: Medical admissions were triaged as likely, possible or unlikely COVID-19 based on clinical criteria. Patients triaged as possible COVID-19 underwent FebriDx lateral flow assay on capillary blood, and those positive for myxovirus resistance protein A (a host response protein) were managed as likely COVID-19.

Primary Outcome measures: Diagnostic accuracy (sensitivity, specificity and predictive values) of the algorithm and the FebriDx assay using SARS-CoV-2 RT-PCR from nasopharyngeal swabs as the reference standard.

Results: 4.0% (136) of 3,443 medical admissions had RT-PCR confirmed COVID-19. Prevalence of COVID-19 was 46% (80/175) in those triaged as likely, 4.1% (50/1,225) in possible and 0.3% (6/2,033) in unlikely COVID-19. Using a SARS-CoV-2 RT-PCR reference standard, clinical triage had sensitivity of 96% (95%CI: 91% - 98%) and specificity of 61.5% (95%CI: 59.8% - 63.1%), whilst the triage algorithm including FebriDx had sensitivity of 93% (95%CI: 87% - 96%) and specificity of 86.4% (95%CI: 85.2% - 87.5%). Whilst 2,033 patients were deemed not to require isolation using clinical criteria alone, the addition of FebriDx to clinical triage allowed a further 826 patients to be released from isolation, reducing the need for isolation rooms by 9.5 per day, 95%CI: 8.9 – 10.2. Ten patients missed by the algorithm had mild or asymptomatic COVID-19.

Conclusions: A triage algorithm including the FebriDx assay had good sensitivity and was useful to 'rule-out' COVID-19 among medical admissions to hospital.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Strengths
  - This was a pragmatic study of a large cohort of consecutive medical admissions enabling a real-world evaluation of the utility of the FebriDx point-of-care assay for COVID-19 triage - a novel application.
  - The analyses performed, including estimates of the number of isolation rooms saved and time-to-test result, can inform hospital management when assessing the effectiveness of the FebriDx point-of-care assay for COVID-19 triage in other settings.

- Limitations
  - A single SARS-CoV-2 RT-PCR is an imperfect reference standard for COVID-19 which may impact specificity, and multiple PCR assays were used each with their own performance characteristics.
  - The performance of the triage algorithm and the FebriDx assay may differ when used in other populations depending on the underlying prevalence of COVID-19 or other respiratory pathogens.
  - The clinical triage criteria were adjusted during the study period to reflect evolving national guidance which may limit the reproducibility of our results.

INTRODUCTION

The Coronavirus disease (COVID-19) pandemic, caused by SARS-CoV-2, presents unprecedented challenges for infection prevention and control (IPC) within healthcare facilities worldwide.[1] Transmission may occur via respiratory droplets, fomites, or via airborne routes (following aerosol-generating procedures).[2-4] Prolonged indoor contact increases transmission, and nosocomial transmission is common.[5,6] Respiratory isolation capacity (neutral or negative pressure side-rooms) is easily saturated within healthcare facilities.[1] Decisions to isolate patients in need of admission with suspected or possible COVID-19 must be rapid and accurate to maintain patient flow from emergency departments (EDs), yet minimise risk of nosocomial transmission.

As COVID-19 can present with non-specific symptoms, diagnostic confirmation is often sought by detection of SARS-CoV-2 ribonucleic acid (RNA) by reverse transcription-polymerase chain reaction (RT-PCR) from nasopharyngeal swab (NPS).[7] However, decisions about patient isolation from the ED are usually required before the results of RT-PCR assays are available.[8,9] Even near-patient, rapid RT-PCR platforms with assay run times of 1-2 hours can be quickly overwhelmed, especially during peaks of COVID-19 incidence.[10,11] Multivariable diagnostic risk models, including clinical criteria and thoracic imaging, are not sufficient, but may be useful as a triage test to ration expensive or scarce point-of care assays.[12,13]

FebriDx (Lumos diagnostics, Sarasota, Florida, US) is a lateral flow assay that detects two host response proteins, Myxovirus resistance protein A (MxA, positive if >40ng/mL) and C-reactive protein (CRP, positive if >20mg/L) in capillary blood samples. MxA is an interferon-induced antiviral host response protein that has been studied as a biomarker to differentiate bacterial and viral respiratory infections.[14–17] More recently FebriDx has demonstrated a sensitivity of 93% and specificity of 86% for detecting COVID-19 compared to RT-PCR in hospital inpatients including patients with clinically likely COVID-19 and those without symptoms of COVID-19.[18] FebriDx could be

useful as an early triage tool to identify patients with COVID-19 and help guide isolation and IPC in patients needing admission to hospital.[18–21] We therefore developed and implemented a COVID-19 triage algorithm, supported by FebriDx, to inform patient flow from the ED whilst awaiting RT-PCR results. Here we describe the diagnostic performance of this algorithm compared to SARS-CoV-2 RT-PCR. We also describe the impact on isolation room demand and the time to FebriDx and RT-PCR results.

METHODS

Patient cohort

We utilised data prospectively entered into a COVID-19 triage database and retrospective extraction of clinical and bed allocation data from electronic patient records and hospital IT systems at Northwick Park Hospital, a large district general hospital serving a diverse population in North-West London. Patients were included if they required admission to a medical ward from the ED between 10th August 2020 and 4th November 2020 inclusive and had a valid SARS-CoV-2 RT-PCR result on admission.

Triage Algorithm

On initial assessment in the ED, consecutive medical admissions were categorised by the attending clinician into three categories for their likelihood of COVID-19 (unlikely, possible and likely), using clinical criteria such as clinical history, observations and plain chest radiograph based on Public Health England guidance (Table 1 and Supplementary Table 1).[22] Patients discharged home or admitted under specialties other than medicine and those under sixteen years of age were not triaged using the algorithm and did not receive FebriDx testing, therefore their exclusion is unlikely to be a source of ascertainment bias. Patients with epidemiological risk factors for COVID-19 (eg. recent contact with a COVID-19 case or travel to a high-risk country) were triaged as likely COVID-19. We refer to this stage of the triage algorithm as ‘clinical criteria’.

We evaluated the impact of using FebriDx in a test-to-deisolate strategy amongst patients designated as possibly having COVID-19 after clinical criteria had been applied at initial assessment. Patients in the possible group underwent testing with FebriDx unless they declined or met an exclusion criterion. Patients were excluded from FebriDx testing if they were immunosuppressed or had had symptoms of COVID-19 for more than 10 days (in these situations a measurable Type I or Type III interferon response might not be present in infected individuals, as per manufacturer's guidance). Patients were also excluded if they had a previous diagnosis of COVID-19 (self-reported or confirmed) or required high dependency unit or intensive care unit (HDU/ICU) admission due to the greater infection control consequences of incorrect triage. All patients underwent NPS testing with SARS-CoV-2 RT-PCR, with rapid RT-PCR assays being prioritised for patients in the likely group.

Only patients with confirmed COVID-19 on SARS-CoV-2 RT-PCR were admitted to a COVID-19 cohort area ('COVID ward'). Those triaged as likely, and those triaged as possible with a positive FebriDx or excluded from having a FebriDx test were designated 'Triage Positive' and admitted to an isolation room until PCR results were available. Patients assigned to the unlikely COVID-19 group and those with a negative FebriDx test were designated 'Triage Negative' and admitted to 'non-COVID wards' whilst awaiting SARS-CoV-2 RT-PCR results (Table 1 and Figure 1).

Ethics Approval

FebriDx testing was implemented as part of routine clinical care in response to data on assay performance for COVID-19 and an urgent clinical need.[21] The study was approved by the London North West University Hospitals Trust Research and Development Committee (SE20/069), and given this was a retrospective review using routinely collected clinical data, they deemed formal ethical approval was not required. Results are reported in compliance with STARD and STROBE guidelines

(see supplementary materials). The FebriDx tests were purchased independently from a UK distributer, and the manufacturer had no role in the study conception, design, data analysis or manuscript preparation.

Testing procedures and definitions

The FebriDx assay was performed as per the manufacturer's instructions at the point-of-care by trained ED health-care assistants. In brief, 5µL of capillary blood is placed on the sample window and reagents are released by pressing a button. The result is read after 10 minutes, with a positive result being the presence of a blue line in the control window and a red line in the MxA window (limit of detection 40ng/ml). The results from the CRP window were not used given all patients had laboratory CRP measurements. Staff performing FebriDx had access to clinical information but not SARS CoV-2 RT-PCR results at the time of FebriDx testing. Routine SARS CoV-2 RT-PCR was done on NPS using either the Panther Fusion SARS-CoV-2 (Hologic Inc, CA, USA), Abbott RealTime SARS-CoV-2 (Abbott Park, IL, USA) or an extraction-free SARS-CoV-2 RT-PCR assay developed by Health Services Laboratories (HSL), UK.[23] Rapid RT-PCR assays used were Xpert Xpress SARS-CoV-2 (Cepheid, CA, USA) or SAMBA II SARS-CoV-2 (Diagnostics for the Real World, CA, USA).

Patients were defined as having COVID-19 or not based on the first valid RT-PCR result up to 72 hours after admission. Patients without a valid RT-PCR result or triage status were excluded from the analysis. Vital signs, including National Early Warning Score (NEWS) were recorded on arrival to the ED. All biochemical, haematological and radiological data were from the first results within 48 hours of admission. Thoracic imaging (chest radiographs and CT) were reported and coded based upon guidelines on COVID-19 from the British Society of Thoracic Imaging (BSTI) at the time of reporting by radiologists.[24] Vital status is reported at the time of hospital discharge or data extraction (20th November 2020) for those who were still inpatients.

Data Analysis and Statistical Methods

We evaluated the real-world diagnostic performance (sensitivity, specificity, and positive and negative predictive values with 95% confidence intervals) of the triage algorithm (described above and in Figure 1) using both clinical criteria (described above and in Table 1) and the FebriDx assay in combination compared to SARS-CoV-2 RT-PCR from a single NPS as a reference standard. We also evaluated each stage of the triage algorithm independently, estimating measures of diagnostic performance for triage using clinical criteria alone and the FebriDx assay in patients with possible COVID-19 compared to a SARS-CoV-2 RT-PCR reference standard. Patients with missing RT-PCR or those missing data on triaging were excluded from analysis. We also reported the time from arrival to FebriDx and RT-PCR results. We described the proportion of patients with COVID-19 who were correctly isolated, estimated the number of isolation beds made available by FebriDx testing, and described the patients with COVID-19 who were incorrectly triaged by the algorithm. Basic descriptive statistics were performed, with comparisons made using chi-squared tests for proportions, t-tests for means and Wilcoxon rank sum to compare non-normally distributed populations. Logistic regression was used to compare age and sex adjusted estimates of in-hospital death in each triage group, using complete cases only. Statistical analyses were performed using Stata version 14.0 (StataCorp, LLC, College Station TX). Based on an anticipated sensitivity of 93%, a sample size of 3335 would estimate the sensitivity of the triage algorithm ±5% with alpha 0.05 and prevalence of 3%.

Patient and Public Involvement

There was no patient involvement in the development of the research question, study design or conduct of the study.

RESULTS

Baseline characteristics and COVID-19 diagnosis

Between the 10th August and 4th November 2020, there were 9,645 emergency department visits resulting in further hospital care. Of these, 3,433 (35.6%) were adult medical patients admitted for further treatment, were triaged using the algorithm based on COVID-19 status and had a valid SARS-CoV-2 RT-PCR result (figure 1). 175 (5.1%) patients were triaged as likely COVID-19, 2,033 (59.2%) patients as unlikely COVID-19 and 1,225 (35.7%) patients were triaged into the possible COVID-19 category. Key patient characteristics are given in Table 2.

There were several differences between the three triage groups (Table 2). The likely COVID-19 group were younger, had higher NEWS scores on arrival and more frequently required supplemental oxygen compared to the unlikely group and the possible group ($p<0.02$ for all comparisons). As expected, more patients in the likely COVID-19 group had chest radiograph changes typical for COVID-19 than in the possible ($p<0.001$), and the unlikely COVID-19 group ($p<0.001$). The possible COVID-19 group were older than the other two groups and were more likely to have an elevated neutrophil count than the likely or possible groups.

Overall, 136/3,443 admissions (4.0%) were diagnosed with PCR-confirmed COVID-19. Prevalence of COVID-19 was 46% (80/175) in likely patients, and 4.1% (50/1,225) in the possible group. Of those triaged as unlikely COVID-19, only 6/2,033 (0.3%) were SARS-CoV-2 RT-PCR positive.

Performance of FebriDx and triage algorithm

The overall diagnostic performance of the clinical triage algorithm compared to the reference standard of SARS-CoV-2 RT-PCR is summarised in table 3. 958 (78.2%) patients in the possible group were tested using FebriDx (those excluded are detailed in figure 1). 13.8% (132/958) of FebriDx test results were positive for MxA, with 86.2% negative and no invalid results. The median duration of

COVID-19 symptoms in patients tested by FebriDx was 2 days (IQR 1-3, n=847). Patients with positive FebriDx results were younger, more likely to be febrile and less likely to have raised neutrophil counts than FebriDx negative patients (supplementary table 2).

31% (41/132) of patients with a positive FebriDx had a positive SARS-CoV-2 RT-PCR, whilst only 4/826 (0.5%) with a negative FebriDx were diagnosed as having COVID-19. All 4 patients with false-negative FebriDx results had normal chest radiographs. 2 patients tested negative for COVID-19 by SARS-CoV-2 RT-PCR but had positive FebriDx results and chest radiograph appearances typical for COVID-19. In the possible COVID-19 group, FebriDx results were available a median of 2.2 hours (IQR: 1.4 to 3.1, n=808) and RT-PCR results a median of 17.8 hours (IQR: 11.4 – 25.3, n=456) after arrival to the ED (figure 2). 88.0% of FebriDx results were available within 4 hours of arrival (n=808).

The triage algorithm correctly identified 126/136 patients with PCR-confirmed COVID-19 in the likely group (sensitivity 93%, 95%CI: 87 - 96) (table 3). The 10 patients who were SARS-CoV-2 RT-PCR positive but missed by the triage algorithm are described in supplementary table 3. 6/10 were classified as unlikely, and 4/10 were classified as possible COVID-19 and had a negative FebriDx. 2/10 were febrile on admission, none required supplemental oxygen, length of stay was short (median 2 days) and 8 had normal chest radiographs (2 did not have thoracic imaging done). Specificity of the algorithm was 86.4% (85.2 - 87.5), and negative predictive value was 99.7% (99.4 - 99.8). Although changes were made to clinical triage criteria during the study period (supplementary table 1), our estimates of diagnostic performance were comparable after excluding individuals who arrived before the last alteration (supplementary table 4).

Outcomes

95% (129/136) of patients with COVID-19 were appropriately managed in isolation rooms or COVID cohort wards as a result of the triage algorithm (supplementary table 5). Of the 10 patients with

PCR-confirmed COVID-19 not identified by the triage algorithm, 7 were initially managed in a non-COVID ward. Had all patients been isolated until SARS-CoV-2 RT-PCR result was available (ie without using clinical criteria or FebriDx to de-isolate) 2,859 more isolation rooms would have been used. When using the triage algorithm, clinical criteria allowed 2,033 patients to be released from isolation after being classified as unlikely COVID-19. The addition of FebriDx to clinical triage allowed 826 more patients to be managed in 'non-COVID' wards than if all patients triaged possible COVID-19 had required isolation (9.5 isolation rooms saved per day, 95%CI: 8.9 – 10.2).

11 (8%) patients with COVID-19 died compared to 150 (4.5%) without COVID-19 (p=0.042). Age and sex adjusted odds of death during the admission were higher for patients in the likely (OR: 3.42, 95% CI: 1.81 - 6.45) and possible groups (OR: 2.44, 95% CI: 1.73 - 3.44) than the unlikely COVID-19 group.

DISCUSSION

Our main findings are that a pragmatic triage algorithm using simple clinical parameters available within the ED and the FebriDx point-of-care test had good sensitivity (93%) and excellent NPV (99.7%) for COVID-19 diagnosed by RT-PCR. Inclusion of FebriDx improved the specificity of triage with minimal reductions in sensitivity, allowing a substantial reduction in the number of isolation rooms needed.

Although clinicians were able to identify patients likely and unlikely to have COVID-19 (46% and 0.3% of whom had confirmed COVID-19 respectively) based on clinical assessment, radiology and basic blood tests, their assessment was not sufficiently specific. The group of patients identified as 'possible' COVID-19 had a 4% prevalence of COVID-19, high mortality and was large enough to overwhelm isolation room capacity. We demonstrate a simple, rapid test performed at the point-of-care can help further risk stratify this group. In real-life settings in a busy ED, a point-of-care test was able to inform isolation decisions within 4 hours of arrival compared to PCR results which were too slow to inform patient flow from ED, even when using 'rapid' PCR assays. Although formal cost-effectiveness analysis was not performed, each FebriDx test only costs about US$18, and this may lead to cost savings.

The strengths of this study are its pragmatic design under routine clinical settings, and that we are able to account for over 95% of medical admissions, reducing risks of bias. There are, however, several limitations. A single SARS-CoV-2 RT-PCR is an imperfect reference standard, and does not account for RT-PCR negative COVID-19 patients. We used multiple RT-PCR platforms, which will have different PCR targets and performance. 10% of patients in the possible group did not get tested with FebriDx for unclear reasons, which could be a source of bias unless these were unavoidable random losses in a busy ED department. The prevalence of COVID-19 was 4.0% in this cohort, and it is

unclear what impact a higher prevalence of COVID-19 or other respiratory pathogens such as influenza would have on these findings. The criteria for likely and possible COVID-19 groups changed during the study period, although this is unlikely to significantly alter the outcomes.

These data build on previous studies of FebriDx showing good sensitivity, and utility as a 'rule-out' test for COVID-19.[17–20] In our pragmatic, 'real-world' study clinical triage by ED clinicians was imperfect. For example, two PCR positive patients were incorrectly classified as 'unlikely' COVID-19 given they had a temperature of >38ºC on arrival (supplementary table 3). The estimate of sensitivity of FebriDx for detecting COVID-19 in our cohort is lower than previously described, likely because our testing strategy differs in that it does not include patients deemed likely to have COVID-19 by clinical criteria. Testing this group would have been unlikely to alter clinical decisions, even if FebriDx had been negative, given the high pre-test probability. The FebriDx test allowed patients with possible COVID-19 to be divided into two groups with similar characteristics and clinical features, but vastly different COVID-19 prevalence (0.5% in FebriDx negative, and 31% in FebriDx positive). However, about 10% of patients in this group were not eligible for FebriDx testing, and had to be managed in isolation rooms as triage-positive patients (see Figure 1).

Only ten patients with COVID-19 were incorrectly triaged by the algorithm, four of whom were tested and 'missed' using FebriDx. These patients were younger, less symptomatic, did not have chest radiograph changes, and mostly likely had mild or asymptomatic COVID-19 infection. Given that MxA is an intracellular GTPase induced by type I and type III interferon responses, it is plausible that sensitivity would be lower in oligo- or asymptomatic infection.[25] Although the patients missed by the algorithm are potential sources of nosocomial transmission, asymptomatic disease is thought to be less transmissible.[26] We found no nosocomial cases related to these patients.

In conclusion, we demonstrate that a simple triage system including the novel FebriDx point-of-care test had good sensitivity and negative predictive value for COVID-19 and utility for managing medical admissions from the ED.

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Author contributions

HH, AGW, LJ, SF, JBL, JR, N Vaughan, N Vaid, GGR, and AKA made substantial contribution to the conception of the work. HH, AGW, LJ, and GD made substantial contribution to the design of the work. HH, GD, SN, KS, SP, MGD, and MT contributed to data acquisition. HH and AGW analysed the data. HH, AGW and LJ contributed to data interpretation. HH and AGW drafted the manuscript. All authors contributed to revising the manuscript critically for important intellectual content, approved the final manuscript and are accountable for all aspects of the work.

Competing interests statement

The authors have no competing interests to declare.

Data availability statement

Data are available upon reasonable request, subject to approval by the London North West University Healthcare NHS Trust Research and Governance Department and approval from relevant ethics and regulatory bodies.

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Tables

COVID-19 triage category	Clinical Criteria	Diagnostics performed in ED	Bed Allocation from ED
Likely	Recent Contact with a confirmed COVID-19 case OR Travel to High Risk country within the last 14 days	Routine RT-PCR	Isolation Room
	Known COVID-19 illness confirmed within the last 14 days prior to current attendance	Urgent RT-PCR	COVID-19 cohort ward or isolation room
	High Clinical Suspicion (eg. Oxygen Requirement, Bilateral infiltrates, Normal WCC/high CRP) OR Change in Normal sense of Smell or Taste		Isolation Room
Possible	Clinical or Radiological Pneumonia OR Fever / Persistent Cough / Shortness of Breath / Hypoxia / Diarrhoea / Confusion	FebriDx * & Urgent RT-PCR	**FebriDx Positive (or not done) → Isolation Room**
			FebriDx Negative → Non-COVID ward
Unlikely	None of the Above	Routine RT-PCR	Non-COVID ward

Table 1. Clinical Criteria for determining triage groups, testing strategy and bed allocation from the Emergency Department prior to RT-PCR result. Clinical criteria for determining triage groups are shown as of 08/10/2020. Changes to these criteria over time are detailed in supplementary table 1. * Patients were excluded from FebriDx testing if they had a prior history of COVID-19, were immunosuppressed, required intensive care or high dependency unit admission, or had had COVID-19 symptoms for > 10 days. RT-PCR=Reverse transcription polymerase chain reaction, ED=Emergency department

Variable	Unlikely	Possible	Likely
N	2033	1225	175
Age (years) median (IQR)	69 (49, 82)	75 (60, 84)	62 (48, 74)
Age over 65 years, n (%, 95%CI)	1128 (55.5%, 53.3; 57.6)	846 (69.1%, 66.5; 71.6)	79 (45%, 38; 53)
Female Sex, n (%, 95%CI)	969 (47.7%, 45.5; 49.8)	603 (49.2%, 46.4; 52.0)	72 (41%, 34; 48)
Male Sex, n (%, 95%CI)	1064 (52.3%, 50.2; 54.5)	622 (50.8%, 48.0; 53.6)	103 (59%, 52; 66)
NEWS, median (IQR)	1 (0, 3)	4 (2, 6)	5 (3, 7)
Respiratory Rate (breaths/min), median (IQR)	18 (18, 20)	24 (20, 28)	24 (21, 32)
SpO2 <94%, n (%, 95%CI)	61 (3.1%, 2.4; 3.9)	234 (19.5%, 17.3; 21.8)	38 (22%, 17; 29)
Required Supplemental Oxygen, n (%, 95%CI)	52 (2.7%, 2.0; 3.4)	245 (20.4%, 18.1; 22.7)	52 (30%, 24; 38)
Temperature >37.5ºC, n (%, 95%CI)	172 (8.8%, 7.6; 10.1)	359 (30.0%, 27.4; 32.6)	73 (43%, 35; 50)
Chest Radiograph - Normal, n (%, 95%CI)	1171 (81.0%, 79.0; 83.0)	537 (49.9%, 46.9; 52.9)	42 (30%, 22; 37)
Chest Radiograph - Typical for COVID-19, n (%, 95%CI)	4 (0.3%, 0.0; 0.5)	25 (2.3%, 1.4; 3.2)	54 (38%, 30; 46)
Chest Radiograph - Other, n (%, 95%CI)	271 (18.7%, 16.7; 20.8)	514 (47.8%, 44.8; 50.8)	45 (32%, 24; 40)
Chest CT - Normal, n (%, 95%CI)	8 (24%, 12; 41)	9 (16%, 9; 29)	0 (0%, 0; 0)
Chest CT - Typical for COVID-19, n (%, 95%CI)	0 (0%, 0; 0)	3 (5%, 2; 16)	3 (43%, 10; 83)
Chest CT - Other, n (%, 95%CI)	26 (76%, 59; 88)	43 (78%, 65; 87)	4 (57%, 17; 90)
CRP (mg/L), median (IQR)	5.7 (1.4, 26.9)	26.4 (7.05, 87.65)	53.7 (25.9, 122.7)
CRP >20mg/L, n (%, 95%CI)	545 (28.7%, 26.7; 30.7)	656 (55.8%, 52.9; 58.6)	134 (80%, 74; 86)
Lymphocyte Count <1.0x10^9/l, n (%, 95%CI)	373 (25.3%, 23.1; 27.5)	383 (43.9%, 40.6; 47.2)	70 (55%, 46; 63)
Neutrophil Count >7.5x10^9/l, n (%, 95%CI)	620 (32.0%, 29.9; 34.0)	598 (50.4%, 47.6; 53.3)	61 (36%, 29; 43)
Crude In Hospital Mortality, n (%, 95%CI)	57 (2.8%, 2.1; 3.6)	89 (7.5%, 6.0; 9.0)	13 (8%, 4; 12)
SARS-CoV-2 RNA Detectable on RT-PCR, n (%, 95%CI)	6 (0.3%, 0.1; 0.5)	50 (4.1%, 3.0; 5.2)	80 (46%, 38; 53)

Table 2: Baseline characteristics, vital signs, initial investigations, mortality and SARS-CoV-2 RT-PCR results for patients in the unlikely, possible and likely COVID-19 groups. For observations on arrival, 3.2 to 4.1% of data were missing. Data were missing for 5.5% of CRP results and 4.0% of haematology results, 22.4% of chest radiograph reports and 2.1% of vital status. 96 patients (2.8%) had a chest CT report available. Imaging reports were coded as per BSTI guidelines. Chest Radiograph reports were coded as: CVCX0 = Normal; CVCX1 = Typical; CVCX2 = Indeterminate; CVCX3 = Non-COVID-19. Chest CT

reports were coded as: CVCT0= Normal; CVCT1= Typical; CVCT2= Indeterminate; CVCT3= Non-COVID-19. IQR=Inter-quartile range, CI=Confidence Interval, NEWS=National Early Warning Score, SpO2=Oxygen Saturations, CRP=C-Reactive Protein, CT=Computerised Tomography

A		SARS-CoV-2 RT-PCR			
		Positive	Negative	Total	
Clinical criteria alone (without FebriDx) (n=3433)	Likely or Possible COVID-19	130	1270	1400	PPV: 9.3% (95% CI: 7.9 – 10.9)
	Unlikely COVID-19	6	2027	2033	NPV: 99.7% (95% CI: 99.3 – 99.9)
	Total	136	3297	3433	
		Sensitivity 96% (95% CI: 91 – 98)	Specificity 61.5% (95% CI: 59.8 – 63.1)		

B		SARS-CoV-2 RT-PCR			
		Positive	Negative	Total	
FebriDx alone in the possible COVID-19 group with FebriDx done. (n=958)	FebriDx Positive	41	91	132	PPV: 31% (95% CI: 24 – 39)
	FebriDx Negative	4	822	826	NPV: 99.5% (95% CI: 98.7 – 99.8)
	Total	45	913	958	
		Sensitivity 91% (95% CI: 78 – 97)	Specificity 90.0% (95% CI: 87.9 – 91.8)		

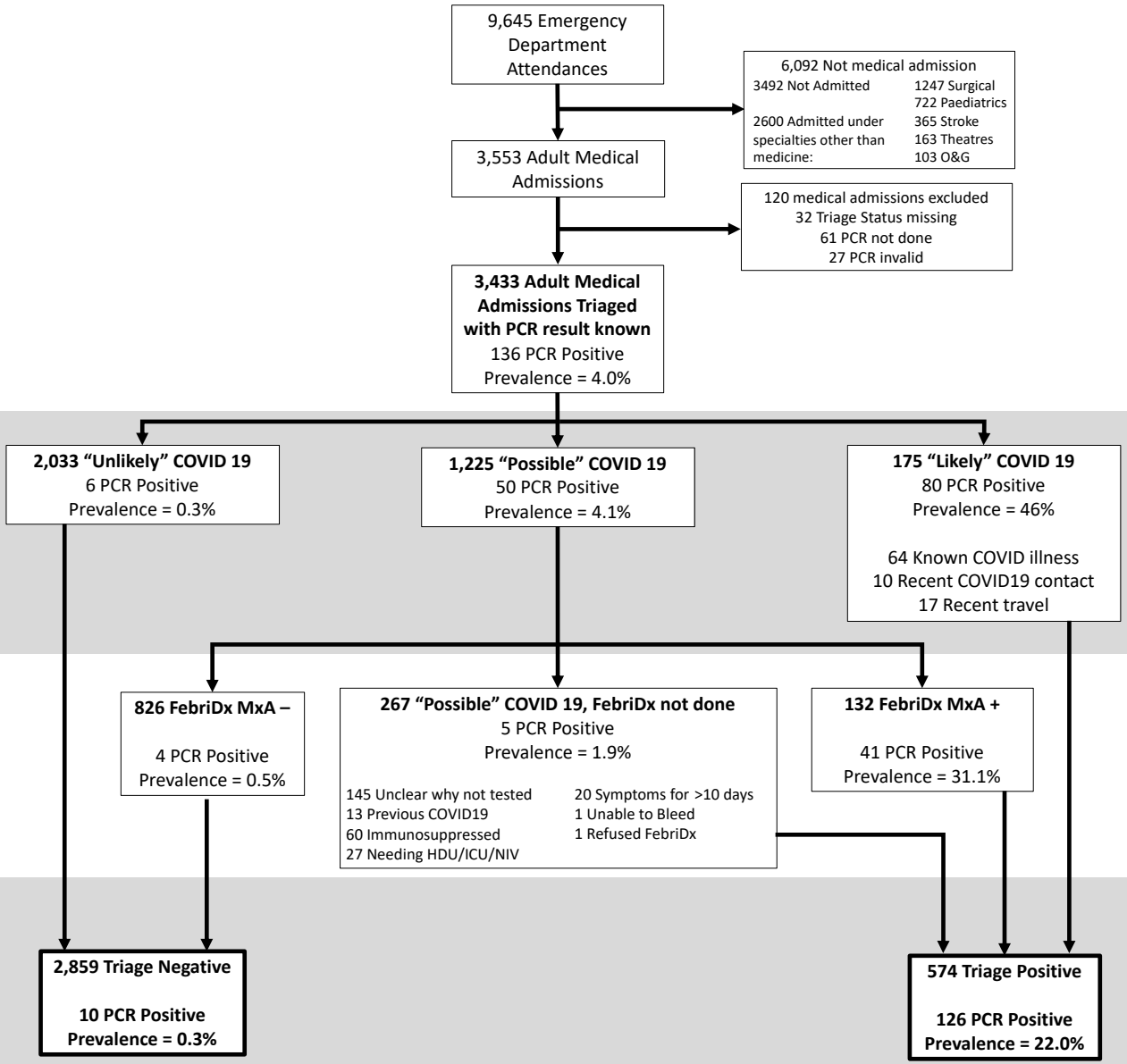
C		SARS-CoV-2 RT-PCR			
		Positive	Negative	Total	
Triage Algorithm using clinical criteria and FebriDx (n=3433)	Triage Positive	126	448	574	PPV: 22% (95% CI: 19 - 26)
	Triage Negative	10	2849	2859	NPV: 99.7% (95% CI: 99.4 - 99.8)
	Total	136	3297	3433	
		Sensitivity 93% (95% CI: 87 - 96)	Specificity 86.4% (95% CI: 85.2 - 87.5)		

Table 3 Cross tabulation of results of the triage algorithm with and without FebriDx as well as the results of FebriDx within the possible COVID-19 group compared to a SARS-CoV-2 RT-PCR reference standard. Measures of Diagnostic Performance are presented for the triage algorithm for the detection of COVID-19: 3A) Using clinical criteria alone without FebriDx, where subjects are classified as positive or negative based on clinical criteria shown in Table 1. Subjects were 'positive' if they were assigned as likely or possible COVID-19 based on clinical criteria alone. 3B) Using the FebriDx assay alone within the possible COVID-19 group receiving a FebriDx test. Subjects are classed as FebriDx positive or negative based on the FebriDx test only. 3C) Using clinical criteria supported by the FebriDx assay. Subjects were classed as Triage positive or negative based on their flow through the algorithm as shown in figure 1. Patients were Triage positive if they were triaged as likely COVID-19 or possible COVID-19 without a negative FebriDx result. Patients were Triage Negative if they were triaged as unlikely COVID-19 or possible COVID-19 with a negative FebriDx result. PPV = Positive Predictive Value, NPV = Negative Predictive Value, CI = Confidence Interval

Figure Legends:

Figure 1: Patient flow through the study and the COVID-19 triage algorithm
Patients were included if they required admission to a medical ward from the ED between 10th August 2020 and 4th November 2020 inclusive. Patients were excluded if they were under sixteen years of age, admitted under specialities other than medicine, or if their triage status or SARS-CoV-2 RT-PCR result was unknown. Counts at each stage of triage are shown in 2x2 tables on the right. These counts correspond with the 2x2 tables and measures of diagnostic performance shown in Table 3. PCR = SARS-CoV-2 RT-PCR.

Figure 2: Time from arrival to the availability of FebriDx and SARS-CoV-2 RT-PCR results
Kernel frequency density plot using the Epanechniko function; Time to FebriDx result was calculated as the time from arrival to the emergency department until the time the FebriDx result was recorded (blue plot), bandwidth=0.3; Time to RT-PCR result was calculated as the time from arrival to to the emergency department until the time the SARS-CoV-2 RT-PCR result was recorded (red plot), bandwidth=2.



		SARS-CoV-2 RT-PCR	
		Positive	Negative
Clinical Criteria Alone	1400 Positive (1225 possible & 175 likely)	130	1270
See Table 3A	2033 Negative (unlikely)	6	2027

		SARS-CoV-2 RT-PCR	
		Positive	Negative
FebriDx Alone	132 FebriDx Positive	41	91
See Table 3B	826 FebriDx Negative	4	822

		SARS-CoV-2 RT-PCR	
		Positive	Negative
Triage Algorithm using Clinical Criteria and FebriDx	574 Triage Positive	126	448
See Table 3C	2859 Triage Negative	10	2849

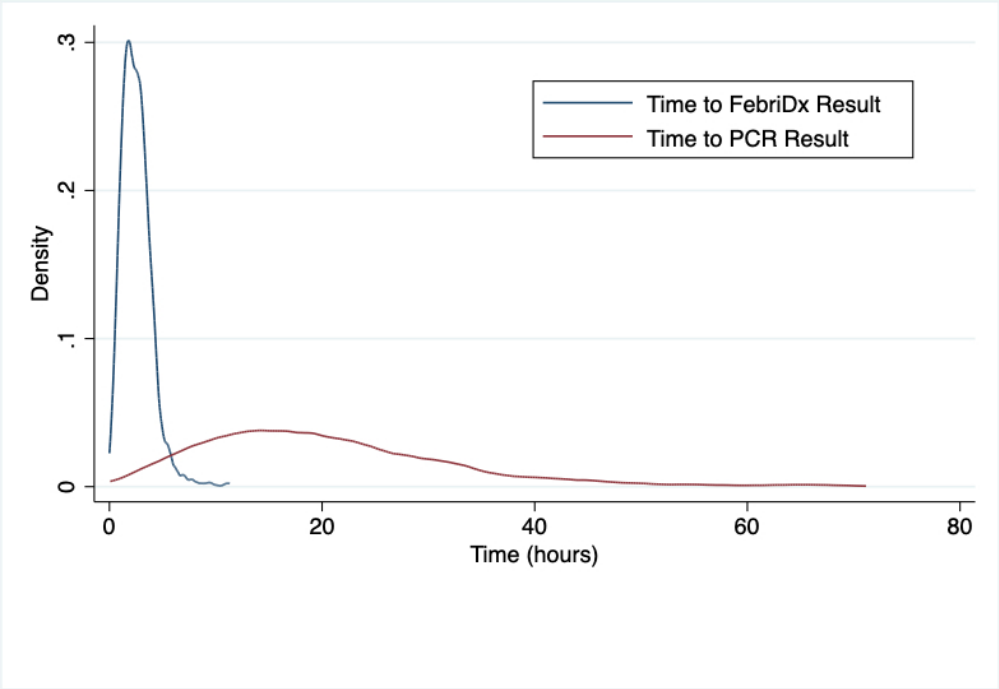


Figure 2

276x191mm (72 x 72 DPI)

Use of the FebriDx point-of-care assay as part of a triage algorithm for medical admissions with possible COVID-19

Supplementary Tables:

Supplementary Table 1: Changes made to the inclusion criteria for the triage categories and the exclusion criteria for FebriDx testing during the study period.

<table>
<tr><td></td><td colspan="4">Date of Update to COVID-19 Triage Criteria</td></tr>
<tr><td></td><td>06/07/2020</td><td>09/09/2020</td><td>21/09/2020</td><td>08/10/2020</td></tr>
<tr><td rowspan="5">Likely</td><td colspan="4">Confirmed COVID-19 during current illness</td></tr>
<tr><td colspan="4">High Clinical Suspicion
(eg. Oxygen Requirement, Bilateral infiltrates, Normal WCC/high CRP)</td></tr>
<tr><td colspan="4">Recent Contact with a confirmed COVID-19 case</td></tr>
<tr><td colspan="4">Travel to High Risk country within the last 14 days</td></tr>
<tr><td colspan="3"></td><td>Change in Normal sense of Smell or Taste</td></tr>
<tr><td rowspan="4">Possible</td><td colspan="3">Change in Normal sense of Smell or Taste</td><td></td></tr>
<tr><td colspan="4">Clinical or Radiological Pneumonia</td></tr>
<tr><td colspan="2">Fever PLUS Persistent Cough OR Shortness of Breath OR Hypoxia</td><td colspan="2">Fever OR Persistent Cough OR Shortness of Breath OR Hypoxia</td></tr>
<tr><td colspan="3"></td><td>Confusion OR Diarrhoea</td></tr>
<tr><td>Unlikely</td><td colspan="4">None of the Above</td></tr>
<tr><td rowspan="4">Exclusion Criteria for FebriDx</td><td colspan="4">Immunosuppressed</td></tr>
<tr><td colspan="4">Previous COVID-19</td></tr>
<tr><td></td><td colspan="3">Requiring ITU/HDU/NIV</td></tr>
<tr><td colspan="2"></td><td colspan="2">COVID-19 Symptoms >10 days</td></tr>
</table>

Supplementary Table 1 footnotes:
The inclusion criteria for the triage categories and the exclusion criteria for FebriDx testing were adjusted during the course of this pragmatic study. WCC=white cell count, CRP= C-Reactive Protein, ITU=Intensive Therapy Unit, HDU=High Dependency Unit, NIV=Non-Invasive ventilation.

Supplementary Table 2: Baseline characteristics, vital signs, initial investigations, mortality and SARS-CoV-2 RT-PCR results for patients in the possible COVID-19 group by FebriDx test result

Variable	FebriDx Negative	FebriDx Positive	FebriDx Not Done
N	826	132	267
Age (years) median (IQR)	77 (61, 85)	69.5 (54.5, 81.5)	72 (60, 81)
Age over 65 years, n (%, 95%CI)	586 (70.9, 67.8; 74.0)	80 (61, 52; 69)	180 (67, 62; 73)
Female Sex, n (%, 95%CI)	399 (48.3, 44.9; 51.7)	63 (48, 39; 56)	141 (53, 47; 59)
Male Sex, n (%, 95%CI)	427 (51.7, 48.3; 55.1)	69 (52, 44; 61)	126 (47, 41; 53)
NEWS, median (IQR)	4 (2, 7)	4 (3, 6)	4 (2, 6)
Respiratory Rate (breaths/min), median (IQR)	24 (20, 28)	24 (20, 28)	24 (19, 28)
SpO2 <94%, n (%, 95%CI)	164 (20.2, 17.6; 23.1)	24 (19, 13; 26)	46 (18, 14; 23)
Required Supplemental Oxygen, n (%, 95%CI)	170 (20.9, 18.2; 23.8)	21 (16, 11; 24)	54 (21, 16; 26)
Temperature >37.5ºC, n (%, 95%CI)	245 (30.2, 27.1; 33.4)	55 (43, 34; 51)	59 (23, 18; 29)
Chest Radiograph - Normal, n (%, 95%CI)	375 (51.2, 47.6; 54.9)	52 (43, 35; 52)	110 (49, 43; 56)
Chest Radiograph - Typical for COVID-19, n (%, 95%CI)	8 (1.1, 0.6; 2.2)	11 (9, 5; 16)	6 (3, 1; 6)
Chest Radiograph - Other, n (%, 95%CI)	349 (47.7, 44.1; 51.3)	57 (48, 39; 57)	108 (48, 42; 55)
Chest CT - Normal, n (%, 95%CI)	9 (20, 10; 34)	0 (0)	0 (0)
Chest CT - Typical for COVID-19, n (%, 95%CI)	2 (4, 1; 17)	0 (0)	1 (17, 1; 81)
Chest CT - Other, n (%, 95%CI)	35 (76, 61; 87)	3 (100)	5 (83, 19; 99)
CRP (mg/L), median (IQR)	26 (7, 96)	37.05 (17.1, 78.9)	18.85 (4.9, 76.3)
CRP >20mg/L, n (%, 95%CI)	443 (55.9, 52.5; 59.4)	87 (67, 58; 75)	126 (50, 43; 56)
Lymphocyte Count <1.0x10^9/l, n (%, 95%CI)	263 (43.8, 39.9; 47.8)	46 (48, 38; 58)	74 (42, 35; 49)
Neutrophil Count >7.5x10^9/l, n (%, 95%CI)	422 (52.8, 49.3; 56.3)	50 (38, 30; 47)	126 (49, 43; 55)
Mortality, n (%, 95%CI)	65 (8.1, 6.4; 10.2)	6 (5, 2; 10)	18 (7, 4; 11)
SARS-CoV2 RNA Detectable on RT-PCR, n (%, 95%CI)	4 (0.5, 0.3; 1.3)	41 (31, 24; 40)	5 (2, 1; 4)

Supplementary Table 2 footnotes: Missing data are summarised in the footnotes to table 2 in the main text. Imaging reports were coded as per BSTI guidelines. Chest Radiograph reports were coded as: CVCX0 = Normal; CVCX1 = Classic; CVCX2 = Indeterminate; CVCX3 = Non-COVID-19. Chest CT reports were coded as: CVCT0= Normal; CVCT1= Classic/probable; CVCT2= Indeterminate; CVCT3= Non-COVID-19. IQR=Inter-quartile range, CI=Confidence Interval, NEWS=National Early Warning Score, SpO2=Oxygen Saturations, CRP=C-Reactive Protein, CT=Computerised Tomography

Supplementary Table 3: Baseline characteristics of patients with positive SARS-CoV-2 RT-PCR results who were classified as triage negative by the algorithm

Case	1	2	3	4	5	6	7	8	9	10
Triage Status	Unlikely						Possible, FebriDx Negative			
Decade of Life*	5	7	3	5	7	6	6	3	7	5
Sex (F/M)	F	M	F	M	M	M	F	M	F	F
Presentation	Fever and epigastric pain	Hypoglycaemic collapse	Hyperkalaemia on clinic bloods	Herpes Zoster	Intentional Overdose	Unstable Angina	URTI symptoms	Diarrhoea	Fever and SOB	Headache and anosmia
Duration of Symptoms (days)	x	x	x	x	x	x	5	7	1	2
NEWS on Arrival	4	1	0	1	2	1	7	2	3	3
Respiratory Rate (breaths/min)	20	18	18	20	14	18	32	18	22	21
SpO2 (%)	97	96	100	96	93	98	94	100	96	100
Required Supplemental Oxygen (Y/N)	N	N	N	N	N	N	N	N	N	N
Temperature ºC	38.1	35.2	36.5	38	36.9	37	39.7	38.3	38.1	36.3
Chest Radiograph	CVCX0	CVCX0	ND	CVCX0	CVCX0	CVCX0	CVCX0	ND	CVCX0	CVCX0
CRP (mg/L)	9.5	2.6	2.6	4	0.7	57.1	16.4	0.9	5.1	68.5
Lymphocyte Count (x10^9/l)	0.5	1.4	2.2	1.1	3	0.7	2.2	1.2	0.5	0.7
Neutrophil Count (x10^9/l)	8.8	9.5	6.5	2.9	2.5	1.9	6.7	2.7	4.6	1.6
Isolated (Y / N)	N	N	N	Y	N	N	N	Y	Y	N
ICU Admission (Y / N)	N	N	N	N	N	N	N	N	N	N
Died (Y / N)	N	N	N	N	N	N	N	N	N	N
Length of stay (days)	2	1	1	1	7	2	4	2	4	1

Supplementary Table 3 footnotes: *Age on arrival is presented in terms of Decade of Life (eg. 5 = age 40 to 49 years).Duration of symptoms was recorded only for patients with a clinical syndrome compatible with COVID-19 tested by FebriDx. Observations presented are those measured on arrival to the Emergency Department. Imaging reports were coded as per BSTI guidelines. Chest Radiograph reports were coded as: CVCX0 = Normal; CVCX1 = Classic;

CVCX2 = Indeterminate; CVCX3 = Non-COVID-19, NEWS=National Early Warning Score, SpO2=Oxygen Saturations, CRP=C-Reactive Protein, Y=Yes, N=No, ND=Not Done

Supplementary Table 4: Cross tabulation of results of the triage algorithm with and without FebriDx as well as the results of FebriDx within the possible COVID-19 group compared to a SARS-CoV-2 RT-PCR reference standard after excluding patients arriving before 08/10/2020.

A		SARS-CoV-2 RT-PCR			
		Positive	Negative	Total	
Clinical criteria alone (without FebriDx) (n=1085)	Likely or Possible COVID-19	82	422	504	PPV: 16.3% (95% CI: 13.3 – 19.8)
	Unlikely COVID-19	0	581	581	NPV: 100% (95% CI: X – X)
	Total	82	1003	1085	
		Sensitivity 100% (95% CI: X – X)	Specificity 57.9% (95% CI: 54.8 – 61.0)		

B		SARS-CoV-2 RT-PCR			
		Positive	Negative	Total	
FebriDx alone in the possible COVID-19 group with FebriDx done. (n=310)	FebriDx Positive	24	39	63	PPV: 38% (95% CI: 27 – 51)
	FebriDx Negative	2	245	247	NPV: 99.2% (95% CI: 96.8 – 99.8)
	Total	26	284	310	
		Sensitivity 92.3% (95% CI: 73.8 – 98.1)	Specificity 86.3% (95% CI: 81.7 – 89.8)		

C		SARS-CoV-2 RT-PCR			
		Positive	Negative	Total	
Triage Algorithm using clinical criteria and FebriDx (n=1085)	Triage Positive	80	177	257	PPV: 31% (95% CI: 26 - 37)
	Triage Negative	2	826	828	NPV: 99.8% (95% CI: 99.0 - 99.9)
	Total	82	1003	1085	
		Sensitivity 97.6% (95% CI: 91 - 99)	Specificity 82.4% (95% CI: 79.9 – 84.6)		

Measures of Diagnostic Performance are presented for the triage algorithm for the detection of COVID-19: 3A) Using clinical criteria alone without FebriDx, where subjects are classified as positive or negative based on clinical criteria shown in Table 1. Subjects were 'positive' if they were assigned as likely or possible COVID-19 based on clinical criteria alone. 3B) Using the FebriDx assay alone within the possible COVID-19 group receiving a FebriDx test. Subjects are classed as FebriDx positive or negative based on the FebriDx test only. 3C) Using clinical criteria supported by the FebriDx assay. Subjects were classed as Triage positive or negative based on their flow through the algorithm as shown in figure 1. Patients were Triage positive if they were triaged as likely COVID-19 or possible COVID-19 without a negative FebriDx result. Patients were Triage Negative if they were triaged as unlikely COVID-19 or possible COVID-19 with a negative FebriDx result. PPV = Positive Predictive Value, NPV = Negative Predictive Value, CI = Confidence Interval

Supplementary Table 5: Actual bed allocation to isolation rooms or COVID-19 cohorts in SARS-CoV-2 RT-PCR positive patients, and those requiring isolation following triage.

	SARS-CoV-2 RT-PCR Positive (n=136)	Triage Positive (n=574)	Likely (n=175)	Possible, FebriDx Positive (n=132)	Possible, FebriDx Not Done (n=267)
'Non-COVID' Ward	7	68	5	4	58
Isolation Room	112	477	152	122	203
COVID-19 Cohort Ward	17	29	18	6	6
% Isolated	95	88.2	97	97	78

Table 4 footnotes: Actual patient movement from the emergency department extracted from the hospital's bed management system.

STARD 2015

AIM

STARD stands for "Standards for Reporting Diagnostic accuracy studies". This list of items was developed to contribute to the completeness and transparency of reporting of diagnostic accuracy studies. Authors can use the list to write informative study reports. Editors and peer-reviewers can use it to evaluate whether the information has been included in manuscripts submitted for publication.

EXPLANATION

A **diagnostic accuracy study** evaluates the ability of one or more medical tests to correctly classify study participants as having a **target condition.** This can be a disease, a disease stage, response or benefit from therapy, or an event or condition in the future. A medical test can be an imaging procedure, a laboratory test, elements from history and physical examination, a combination of these, or any other method for collecting information about the current health status of a patient.

The test whose accuracy is evaluated is called **index test.** A study can evaluate the accuracy of one or more index tests. Evaluating the ability of a medical test to correctly classify patients is typically done by comparing the distribution of the index test results with those of the **reference standard**. The reference standard is the best available method for establishing the presence or absence of the target condition. An accuracy study can rely on one or more reference standards.

If test results are categorized as either positive or negative, the cross tabulation of the index test results against those of the reference standard can be used to estimate the **sensitivity** of the index test (the proportion of participants *with* the target condition who have a positive index test), and its **specificity** (the proportion *without* the target condition who have a negative index test). From this cross tabulation (sometimes referred to as the contingency or "2x2" table), several other accuracy statistics can be estimated, such as the positive and negative **predictive values** of the test. Confidence intervals around estimates of accuracy can then be calculated to quantify the statistical **precision** of the measurements.

If the index test results can take more than two values, categorization of test results as positive or negative requires a **test positivity cut-off**. When multiple such cut-offs can be defined, authors can report a receiver operating characteristic (ROC) curve which graphically represents the combination of sensitivity and specificity for each possible test positivity cut-off. The **area under the ROC curve** informs in a single numerical value about the overall diagnostic accuracy of the index test.

The **intended use** of a medical test can be diagnosis, screening, staging, monitoring, surveillance, prediction or prognosis. The **clinical role** of a test explains its position relative to existing tests in the clinical pathway. A replacement test, for example, replaces an existing test. A triage test is used before an existing test; an add-on test is used after an existing test.

Besides diagnostic accuracy, several other outcomes and statistics may be relevant in the evaluation of medical tests. Medical tests can also be used to classify patients for purposes other than diagnosis, such as staging or prognosis. The STARD list was not explicitly developed for these other outcomes, statistics, and study types, although most STARD items would still apply.

DEVELOPMENT

This STARD list was released in 2015. The 30 items were identified by an international expert group of methodologists, researchers, and editors. The guiding principle in the development of STARD was to select

items that, when reported, would help readers to judge the potential for bias in the study, to appraise the applicability of the study findings and the validity of conclusions and recommendations. The list represents an update of the first version, which was published in 2003.

More information can be found on http://www.equator-network.org/reporting-guidelines/stard.

Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT			**1**
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	1
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	2
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	4
	4	Study objectives and hypotheses	5
METHODS			
Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	5
Participants	**6**	Eligibility criteria	5, table 1 (page 12)
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	5
	8	Where and when potentially eligible participants were identified (setting, location and dates)	5
	9	Whether participants formed a consecutive, random or convenience series	5
Test methods	**10a**	Index test, in sufficient detail to allow replication	6
	10b	Reference standard, in sufficient detail to allow replication	6
	11	Rationale for choosing the reference standard (if alternatives exist)	NA
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	5
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	NA
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	6
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	6
Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy	7
	15	How indeterminate index test or reference standard results were handled	7
	16	How missing data on the index test and reference standard were handled	7
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	NA
	18	Intended sample size and how it was determined	7
RESULTS			
Participants	**19**	Flow of participants, using a diagram	Figure 1 (page 17)
	20	Baseline demographic and clinical characteristics of participants	Table 2 (page 18)

	21a	Distribution of severity of disease in those with the target condition	Table 2 (page 18)
	21b	Distribution of alternative diagnoses in those without the target condition	NA
	22	Time interval and any clinical interventions between index test and reference standard	6
Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	Table 3 (page 20) and Supplementary Table 4
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	Table 3 (page 20)
	25	Any adverse events from performing the index test or the reference standard	NA
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	11
	27	Implications for practice, including the intended use and clinical role of the index test	12
OTHER INFORMATION			
	28	Registration number and name of registry	NA
	29	Where the full study protocol can be accessed	NA
	30	Sources of funding and other support; role of funders	12

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5 and Table 1
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	7
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Figure 1
		(b) Give reasons for non-participation at each stage	Figure 1
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 2

		(b) Indicate number of participants with missing data for each variable of interest	Table 2
		(c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	9

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	8 Table 2 NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Supplementary table 3
Discussion			
Key results	18	Summarise key results with reference to study objectives	Table 3
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.