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ORIGINAL PAPER

Fever as a predictor of adverse outcomes in COVID-19

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Summary

Background/Introduction: There are little data on outcomes of COVID-19 patients with the presence of fever compared to the presence of symptoms.
Aim: We examined the associations between symptomology, presence of fever and outcomes of a COVID-19 cohort.
Design and Methods: Between 23 January and 30 April 2020, 554 COVID-19 patients were admitted to a tertiary hospital in Singapore. They were allocated into four groups based on symptomology and fever—Group 1: asymptomatic and afebrile, Group 2: symptomatic but afebrile, Group 3: febrile but asymptomatic and Group 4: symptomatic and febrile. The primary outcomes were intensive care unit (ICU) admissions and mortality. The composite end-point included ICU admissions, mortality or any COVID-19 related end-organ involvement.
Results: There were differences in ferritin ($P=0.003$), C-reactive protein (CRP) levels ($P<0.001$) and lymphopenia ($P=0.033$) across all groups, with the most favourable biochemical profile in Group 1, and the least in Group 4. Symptomatic groups (Groups 2 and 4) had higher ICU admissions (1.9% and 6.0%, respectively, $P=0.003$) than asymptomatic groups (Groups 1 and 3). Composite end-point was highest in Group 4 (24.0%), followed by Group 3 (8.6%), Group 2 (4.8%) and Group 1 (2.4%) ($P<0.001$). The presence of fever (OR 4.096, 95% CI 1.737–9.656, $P=0.001$) was associated with the composite end-point after adjusting for age, pulse rate, comorbidities, lymphocyte, ferritin and CRP. Presence of symptoms was not associated with the composite end-point.
Discussion/Conclusion: In this COVID-19 cohort, presence of fever was a predictor of adverse outcomes. This has implications on the management of febrile but asymptomatic COVID-19 patients.

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Introduction

The rapid spread of coronavirus disease 2019 (COVID-19) has caused significant morbidity and mortality worldwide.[1,2] Many countries have adopted community surveillance strategies involving temperature screening and routine questions for the presence of symptoms. International data have demonstrated that asymptomatic infections account for up to 60% of all infections.[1,3]

The initial presentation of COVID-19 patients varies from being completely asymptomatic, to having mild upper respiratory symptoms, to acute respiratory distress syndrome (ARDS). Older age is a risk factor for severe COVID-19 infection. On the other hand, younger people tend to present with only milder symptoms or are asymptomatic.[4,5] As these cases are difficult to identify, suppressing asymptomatic transmission remains a challenge.

Singapore's migrant labour workforce predominantly resides in densely populated, purpose-built foreign worker dormitories. Initial outbreaks linked to importation and community spread were curtailed through border control and social distancing measures,[6,7] but clusters of outbreaks in foreign worker dormitories proved more challenging to control. These clusters contributed to the majority of Singapore cases as identified by active case finding of dormitory residents.[8,9] During the early phases of the foreign worker dormitory outbreak, all swab-positive patients were admitted to hospital for monitoring and risk assessment prior to transfer of low-risk cases to a non-hospital facility for isolation. This policy allowed the unique opportunity to characterize and evaluates a large number of COVID-19 patients, with or without the presence of fever.[10]

Given the current challenges faced with asymptomatic COVID-19 transmission, there is an urgent need to understand the symptomatology, the clinical and biochemical profiles and outcomes of these asymptomatic or mildly symptomatic patients. This study aims to examine and compare the four major groups of COVID-19 patients in a relatively young, low-risk population—those who presented (i) asymptomatic and afebrile, (ii) symptomatic but afebrile, (iii) febrile but asymptomatic and (iv) both symptomatic and febrile.

Materials and methods

Study population

Between 23 January and 30 April 2020, 554 consecutive patients who were diagnosed with COVID-19 were admitted to a tertiary academic healthcare institution in Singapore. Confirmed COVID-19 cases were defined as those with a positive polymerase chain reaction test via a nasopharyngeal swab. All confirmed COVID-19 patients were included in this study regardless of the exposure history (i.e. imported cases from overseas travel, local community cases or from the foreign worker dormitory). Demographic, past medical history, symptom prevalence, clinical examination, biochemical data, electrocardiogram, medicine administration records and clinical outcomes were collected retrospectively from the electronic health records. Of note, Lopinavir/Ritonavir and Remdesivir were used in some patients as part of a clinical trial. These patients were followed up from their admission to the discharge date. This study was conducted in accordance with the revised Declaration of Helsinki and approved by the institutional and local ethics committee (NHG DSRB 2020/00545).

Allocation into study groups

On admission to hospital, patients were assessed by a physician at the emergency department for risk factors, symptoms and vital signs. Patients who were defined as a symptomatic COVID-19 case displayed one or more of the following symptoms on arrival, within a day of the nasopharyngeal nucleic acid test: breathlessness, cough, rhinorrhoea, blocked nose, anosmia, fatigue, myalgia, headache, sore throat, headache, nausea or vomiting, abdominal pain and diarrhoea. An asymptomatic COVID-19 case was defined as a patient who reported no physical symptoms within the last 2 weeks, but with a positive nucleic acid test. Fever was defined as having an axillary temperature of $\geq$38°C within the first 24 h of admission. The post-illness onset was assessed as the time interval from symptom onset to hospital admission; or in the absence of symptoms, the date of the positive nucleic acid test. Serial blood tests were done based on the discretion of the attending physician; of which, the first two consecutive sets of blood tests were recorded in the study—the first set on admission day and the second on subsequent days.

These patients were then allocated into four groups. The first group (asymptomatic and afebrile) consisted of those who reported the absence of symptoms and were afebrile on admission. The second group (symptomatic but afebrile) consisted of those who reported one or more of the listed symptoms, but were afebrile on admission. The third group comprised of those who reported absence of symptoms but were febrile on admission. The fourth group included those who had one or more of the listed symptoms and were febrile on admission.

Study outcomes

The primary outcomes of the study were intensive care unit (ICU) admissions and in-hospital mortality. Other outcomes included supplementary oxygen requirement or need for mechanical ventilation, as well as COVID-related end-organ manifestations, such as pneumonia, ARDS, acute kidney injury (AKI), pulmonary embolism, coagulopathy, acute myocardial infarction, ventricular tachycardia, myocardial injury or myocarditis, heart failure and stroke.[11–14] These end-points were chosen as they would generally require hospitalization under normal circumstances. The study composite end-point was the presence of one of the following: ICU admissions, mortality, requiring supplementary oxygen or mechanical ventilation or one of the COVID-related conditions listed above.

Statistical analysis

Categorical variables were expressed as absolute values (and percentages), whilst continuous variables were expressed as mean value $\pm$1 SD. One-way analysis of variance was used to examine the association between continuous data, and Pearson's chi-square test (or Fisher's exact test where appropriate) were used to evaluate categorical variables. Multivariable logistic regression analysis was performed in order to identify independent factors associated with each subgroup of study participants. The multivariable model included important clinical and biochemical variables that were significant on univariable analysis. A P-value of <0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp, Armonk, NY).

Results

Baseline demographics and risk factors

Of the 554 study participants, 41 (7.4%) were allocated to Group 1 (asymptomatic and afebrile group), 311 (56.1%) to Group 2 (symptomatic but afebrile), 35 (6.3%) to Group 3 (febrile but asymptomatic) and 167 (30.2%) in Group 4 (symptomatic and febrile).

Across the four groups, participants in Group 1 were the youngest, followed by participants in Group 2 and 3, and participants in Group 4. In terms of exposure history, imported cases and local community cases tended to be in the symptomatic groups (Groups 2 and 4). Foreign dormitory workers made up the majority of patients in all four groups.

With regards to the presence of medical comorbidities, symptomatic individuals in Groups 2 and 4 had a higher prevalence of comorbidities in general, with significantly more having hypertension and hyperlipidaemia. All patients with two or more comorbidities were symptomatic whether or not fever was present.

The differences in baseline demographics and characteristics of the study cohort are displayed in Table 1.

Symptom prevalence

Out of 554 patients, 478 had symptoms (86.3%) on admission. The majority of patients had respiratory symptoms such as cough, followed by sore throat, myalgia and rhinorrhoea (supplementary figure S1).

Differences in clinical profile and laboratory investigations

Patients who were febrile on admission had significantly lower lymphocyte counts (P=0.033) and platelet counts (P=0.001) compared to those who were afebrile. There were significantly higher neutrophil–lymphocyte and platelet–lymphocyte ratios (both P<0.001) in the two febrile groups compared to the afebrile groups. In terms of inflammatory markers, patients with the presence of both fever and symptoms had significantly higher C-reactive protein (CRP) levels, followed by patients with either the presence of fever or symptoms (Groups 2 and 3), and subsequently those with neither fever nor symptoms (Group 1) (P<0.001). Similarly, the highest ferritin levels were found in Group 4 patients (P=0.003). The rest of the clinical and laboratory findings are displayed in Table 2.

Figure 1 displays the trends of pulse rates, ferritin levels, lymphocyte counts and CRP levels according to the four groups across the different time points. The admission pulse rates were higher in the febrile groups compared to the afebrile groups. Similarly, the mean CRP levels were highest in the febrile groups compared to the afebrile groups on the first set of blood test, with an overall increase in CRP across all four groups in the second set of blood test. In keeping with the inflammatory response, the mean ferritin levels were highest in Group 4, with an overall increase in ferritin levels across the four groups on the second set of blood test. In a similar trend, the mean lymphocyte counts were lower in the febrile groups (3 and 4) compared to the afebrile groups, with further decrease in the mean lymphocyte counts on the second set of blood test across the four groups.

The symptomatic and febrile group had the highest heart rates, while the asymptomatic groups (Groups 1 and 2) had the lowest, which was in keeping with the extent of the inflammatory response (Table 2).

Intravenous fluids, intravenous antibiotics, Lopinavir/Ritonavir and Remdesivir were used primarily in the symptomatic groups (Groups 2 and 4). Patients who were febrile but asymptomatic did not receive any form of the listed treatments (supplementary table S1).

Differences in study outcomes

In terms of end-organ involvement, the incidence of COVID-19 pneumonia was highest in the febrile groups (Group 4: 20.4%, Group 3: 8.6%), followed by the afebrile groups (Group 2: 6.1%, Group 1: 2.4%) (P<0.001). There was significantly higher incidence of ARDS in symptomatic patients (Group 4, 3.8%; Group 2; 1.3%, P=0.041). The incidence of AKI was significantly highest in Group 4 (17.4%, P<0.001). There were significantly increased rates of pulmonary embolism and coagulopathy in Group 4 patients. Of note, there were no differences across all groups in terms of cardiovascular complications, such as acute myocardial infarction, ventricular tachycardia, myocarditis or heart failure.

Figure 2 displays the time-dependent covariate analysis of the length of stay and the proportion of patients remaining in hospital across the four groups. There is significant difference in the proportion of patients remaining in hospital (Log-rank 7.9, P=0.048), with the highest proportion of patients Group 4 remaining in hospital within 14 days of admission. However, patients in Groups 1 and 3 who were not discharged within 2 weeks of admission tended to stay longer (n=17, mean 32±10 days); none of whom suffered from the study composite end-point. The reasons for the prolonged stay for Groups 1 and 3 patients included the lack of space and availability in discharge isolation facilities.

With regards to the primary outcomes, significantly higher rates of ICU admissions were observed in the symptomatic groups (Group 4, 7.8%; Group 2; 1.9%, P=0.003), but no ICU admissions observed in the asymptomatic groups (Groups 1 and 3). Group 4 patients had significantly higher rates of requiring supplementary oxygen on the general ward and mechanical ventilation in the ICU, followed by Group 2 patients. Again, asymptomatic patients in Groups 1 and 3 did not require supplementary oxygen or mechanical ventilation.

There was a trend towards increased all-cause mortality (1.7%, P=0.185) in the group with symptomatic and febrile patients. No deaths were reported in the other three groups. Composite study end-point was significantly highest in patients with symptoms and fever (24.0%), followed by those with fever alone (8.6%), symptoms alone (4.8%) and those without symptoms or fever (2.4%, P<0.001).

Independent clinical predictors for composite end-point and for each subgroup of study participants

Univariable analysis demonstrated that age [odds ratio (OR) 1.067, 95% confidence interval (95% CI) 1.044–1.090, P<0.001], presence of fever (OR 5.679, 95% CI 3.104–10.391, P<0.001), presence of comorbidities (OR 5.258, 95% CI 2.032–8.923, P<0.001), lymphopenia (OR 0.2777, 95% CI 0.167–0.458, P<0.001), high ferritin (OR 1.002, 95% CI 1.001–1.003, P<0.001) and high CRP (OR 1.022, 95% CI 1.013–1.031, P<0.001) were significantly associated with composite study end-point. However, the presence of symptoms did not display significant association with the composite outcome. Multivariable analysis revealed that the

Table 1. Differences in demographics and baseline characteristics of COVID-19 patients according to symptom and admission fever profile (*N*=554)

	Group 1: asymptomatic and afebrile (*N*=41)	Group 2: symptomatic but afebrile (*N*=311)	Group 3: febrile but asymptomatic (*N*=35)	Group 4: symptomatic and febrile (*N*=167)	*P*-value
Age (years)	33 (11)	36 (11)	35 (8)	40 (12)	<0.001
Sex (male)	41 (100)	261 (84)	31 (91)	145 (88)	0.031
Ethnicity					0.002
Chinese	2 (4.9)	41 (13.2)	3 (8.6)	45 (26.9)	
Malay	3 (7.3)	25 (8.0)	2 (5.7)	2 (2.4)	
Indian	25 (61.0)	107 (34.4)	11 (31.4)	56 (33.5)	
Bangladeshi	10 (24.4)	93 (29.9)	18 (51.4)	54 (32.3)	
Eurasian	0	2 (0.6)	0	0	
Others	1 (2.4)	12 (3.8)	0	1 (0.6)	
Exposure history					0.022
Imported cases	0	18 (5.8)	0	11 (6.6)	
Local community cases	2 (4.9)	60 (19.3)	3 (8.6)	35 (21.0)	
Foreign dormitory workers	39 (95.1)	233 (74.9)	32 (91.4)	121 (72.5)	
Smoking status					0.552
Non-smoker	37 (92.5)	283 (94.0)	34 (97.1)	147 (93.0)	
Current smoker	2 (5.0)	16 (5.3)	1 (2.9)	11 (7.0)	
Ex-smoker	1 (2.5)	2 (0.7)	0	0	
Risk factor					
Overseas travel	0	19 (6.1)	0	10 (6.0)	0.064
Contact with confirmed COVID-19 case	7 (17.1)	74 (23.8)	5 (14.3)	45 (26.9)	0.163
From COVID-19 cluster, but no known contacts	1 (3.0)	9 (4.3)	1 (3.6)	3 (2.7)	0.900
Foreign worker dormitory	38 (97.4)	215 (88.5)	30 (93.8)	119 (88.1)	0.287
Medical comorbidities					
Hypertension	1 (2.6)	25 (10.7)	2 (7.1)	25 (18.9)	0.019
Hyperlipidaemia	0	15 (6.6)	0	19 (14.8)	0.002
Diabetes mellitus	0	13 (5.7)	0	8 (6.6)	0.229
Asthma	0	4 (1.8)	1 (3.6)	1 (0.8)	0.593
Obstructive sleep apnea	0	0	0	3 (2.5)	0.065
Ischemic heart disease	0	4 (1.8)	0	1 (0.8)	0.671
Congestive heart failure	0	3 (1.3)	0	0	0.474
Stroke	0	2 (0.9)	0	0	0.641
Chronic kidney disease	0	2 (0.8)	0	1 (0.8)	0.962
Fatty liver	0	1 (0.4)	0	2 (1.7)	0.543
Presence of comorbidities					0.125
0	40 (97.6)	292 (93.9)	32 (91.4)	150 (89.8)	
1	1 (2.4)	8 (2.6)	3 (8.6)	6 (3.6)	
≥2	0	11 (3.5)	0	11 (6.6)	

presence of fever remained an independent clinical predictor of the study composite outcome after adjusting for the confounders (OR 4.096, 95% CI 1.737–9.656, *P*=0.001) (Table 3).

In terms of subgroup analysis, multivariable analysis identified a lower lymphocyte count (i.e. more profound lymphopenia) as the independent clinical factor associated with patients who were febrile but asymptomatic (OR 0.279, 95% CI 0.139–0.559, *P*<0.001). On the other hand, an increased admission pulse rate (OR 1.046, 95% CI 1.032–1.060, *P*<0.001), increased CRP (OR 1.012, 95% CI 1.002–1.022) and decreased eGFR (OR 0.970, 95% CI 0.953–0.966, *P*<0.001) were independent factors associated in the group of patients who were symptomatic and febrile. Of note, there was a trend towards increased ferritin in Group 4 patients, but this did not reach statistical significance. On the contrary, patients who were symptomatic but afebrile had lower admission pulse rate (OR 0.964, 95% CI 0.953–0.976, *P*<0.001), but did not have associated raised inflammatory markers as compared to their counterparts. No significant clinical predictors were demonstrated in Group 1 patients (supplementary table S2).

In the subgroup analysis of patients with fever (*n*=202), there were no independent predictors of the composite study end-point in the multivariable analysis, which included the following variables: admission pulse rate (OR 1.008, 95% CI 0.987–1.030, *P*=0.463), age (OR 1.037, 95% CI 0.993–1.083), lymphocyte count (OR 0.888, 95% CI 0.490–1.609, *P*=0.696), CRP (OR 1.012, 95% CI 0.999–1.024, *P*=0.809) and ferritin (OR 1.000, 95% CI 0.999–1.002, *P*=0.809).

Discussion

The main findings of this study were (i) asymptomatic and afebrile COVID-19 positive patients had more favourable clinical and biochemical inflammatory response and the lowest rates of COVID-19 related end-organ damage. (ii) On the contrary, symptomatic and febrile COVID-19 patients generally had the least

Table 2. The clinical profile, laboratory, electrocardiogram findings and clinical outcomes of COVID-19 patients according to symptom and admission fever profile (N=554)

	Group 1: asymptomatic and afebrile (N=41)	Group 2: symptomatic but afebrile (N=311)	Group 3: febrile but asymptomatic (N=35)	Group 4: symptomatic and febrile (N=167)	P-value
Clinical profile					
Day of illness at presentation	N.A.	3 (4)	2 (5)	4 (6)	0.150
Length of days with fever	0	0	1.6 (1.1)	2.6 (2.5)	<0.001
Admission temperature (°C)	37.0 (0.6)	37.1 (0.5)	38.3 (0.5)	38.3 (0.7)	<0.001
Admission systolic blood pressure (mmHg)	129 (22)	129 (18)	133 (16)	133 (16)	0.104
Admission diastolic blood pressure (mmHg)	82 (12)	80 (13)	84 (9)	81 (12)	0.425
Admission oxygen saturation (%)	98 (1)	98 (2)	98 (1)	97 (3)	0.021
Admission pulse rate (beats per min)	91 (17)	89 (13)	102 (17)	103 (20)	<0.001
Discharge systolic blood pressure (mmHg)	114 (11)	116 (13)	117 (13)	117 (14)	0.462
Discharge diastolic blood pressure (mmHg)	71 (10)	70 (11)	74 (10)	73 (10)	0.090
Discharge pulse rate (beats per min)	74 (15)	76 (12)	75 (12)	75 (11)	0.957
Laboratory investigations					
Leucocyte ($\times 10^9$/l)	6.6 (1.9)	6.4 (2.0)	6.2 (1.6)	6.5 (2.7)	0.864
Neutrophil ($\times 10^9$/l)	3.8 (2.7)	3.7 (2.0)	4.0 (1.4)	4.2 (2.5)	0.101
Eosinophil ($\times 10^9$/l)	0.7 (1.8)	0.6 (1.6)	0.5 (1.6)	0.6 (1.9)	0.962
Lymphocyte ($\times 10^9$/l)	2.2 (1.1)	2.1 (1.6)	1.3 (0.5)	1.7 (2.9)	0.033
Monocyte ($\times 10^9$/l)	0.9 (1.4)	0.7 (0.5)	1.0 (0.3)	1.0 (2.1)	0.071
Haemoglobin (g/dl)	15.3 (1.6)	14.8 (1.7)	15.2 (1.0)	14.7 (1.7)	0.111
Platelet ($\times 10^9$/l)	225 (54)	237 (63)	222 (47)	213 (55)	0.001
Neutrophil–lymphocyte ratio	2.10 (1.83)	2.26 (2.29)	7.00 (22.17)	3.81 (3.68)	<0.001
Platelet–lymphocyte ratio	119.5 (69.6)	136.2 (60.1)	386.3 (1216.0)	177.7 (88.7)	<0.001
Haematocrit (%)	45 (3)	46 (29)	45 (3)	45 (15)	0.962
Sodium (mmol/l)	138 (2)	138 (3)	138 (2)	137 (3)	0.001
Creatinine (mmol/l)	76 (11)	77 (36)	82 (15)	84 (23)	0.108
Estimated glomerular filtration rate (ml/min)	112 (13)	109 (18)	103 (15)	97 (19)	<0.001
Albumin (g/l)	32 (2)	44 (22)	43 (3)	42 (17)	0.830
Total bilirubin (umol/l)	14 (8)	12 (9)	11 (7)	11 (5)	0.160
Aspartate aminotransferase (U/l)	35 (14)	36 (60)	35 (15)	42 (32)	0.713
Alanine aminotransferase (U/l)	43 (27)	45 (48)	47 (37)	47 (43)	0.953
Lactate dehydrogenase (ng/l)	398 (123)	410 (338)	383 (73)	506 (613)	0.102
D-dimer (ug/ml)	0.3 (0.3)	0.7 (0.4)	0.5 (0.2)	2.3 (6.0)	0.873
C-reactive protein (mg/l)	7 (5)	10 (24)	10 (6)	23 (34)	<0.001
Ferritin	165 (169)	156 (162)	137 (72)	234 (309)	0.003
Electrocardiogram					
Ventricular rate (beats per min)	75 (13)	74 (13)	84 (14)	85 (18)	<0.001
PR interval (ms)	151 (31)	161 (123)	144 (18)	149 (23)	0.481
QRS duration (ms)	88 (9)	89 (12)	89 (12)	89 (13)	0.951
Corrected QT interval (ms)	412 (20)	419 (25)	418 (21)	422 (26)	0.168
Presence of ST-segment depression	0	0	0	4 (2.6)	0.025
Rhythm					<0.001
Sinus rhythm	27 (67.5)	224 (77.5)	28 (82.4)	112 (70.9)	
Sinus tachycardia	4 (10.0)	11 (3.8)	3 (8.8)	34 (21.5)	
Sinus bradycardia	9 (22.5)	53 (18.3)	3 (8.8)	12 (7.6)	
Atrial fibrillation	0	1 (0.3)	0	0	
Clinical outcomes					
Pneumonia	1 (2.4)	19 (6.1)	3 (8.6)	34 (20.4)	<0.001
Pleural effusion					0.532
Unilateral	0	0	0	2 (1.3)	
Bilateral	0	1 (0.4)	0	1 (0.6)	
Acute respiratory distress syndrome	0	4 (1.3)	0	8 (4.8)	0.041
Acute kidney injury	1 (2.4)	12 (3.9)	3 (8.6)	29 (17.4)	<0.001
Requiring dialysis	0	3 (1.0)	0	4 (2.4)	0.406
Pulmonary embolism	0	1 (0.4)	0	5 (4.2)	0.035
Coagulopathy	0	0	0	3 (1.8)	0.011
Acute myocardial infarction	0	1 (0.3)	0	0	0.198
Ventricular tachycardia	0	0	0	1 (0.8)	0.487
Myocarditis/myocardial injury	0	2 (0.9)	0	1 (0.8)	0.899
Heart failure	0	1 (0.5)	0	0	0.842

(continued)

Table 2. (continued)

	Group 1: asymptomatic and afebrile (*N*=41)	Group 2: symptomatic but afebrile (*N*=311)	Group 3: febrile but asymptomatic (*N*=35)	Group 4: symptomatic and febrile (*N*=167)	*P*-value
Stroke	0	0	0	1 (0.8)	0.483
Supplementary oxygen on general ward	0	3 (1.0)	0	12 (7.2)	<0.001
Persistent fever >72 h	0	3 (1.0)	3 (8.6)	34 (20.5)	<0.001
Intensive care unit admission	0	6 (1.9)	0	13 (7.8)	0.003
Mechanical ventilation	0	6 (1.9)	0	10 (6.0)	0.029
Inotropes	0	3 (1.3)	0	5 (4.0)	0.203
All-cause mortality	0	0	0	2 (1.7)	0.185
Composite study end-point	1 (2.4)	15 (4.8)	3 (8.6)	40 (24.0)	<0.001

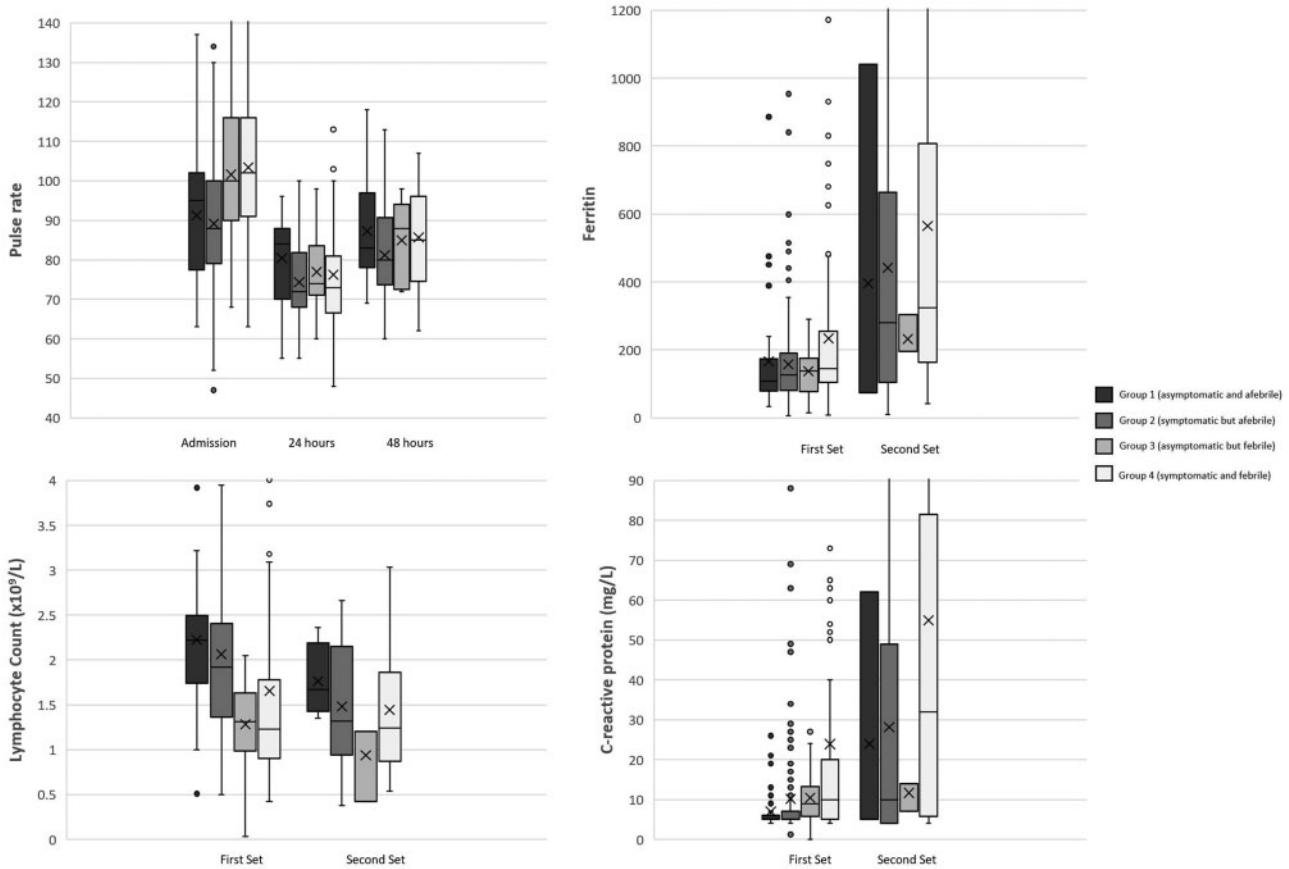

Figure 1. The trend of the mean pulse rate, ferritin levels, lymphocyte count and CRP during the admission categorized according to the four study groups.

favourable biochemical inflammatory response, which were in keeping with the higher rates of the study composite end-point. They had increased risk of COVID-related conditions, such as pneumonia, ARDS, AKI, pulmonary embolism and coagulopathy. (iii) Although patients with either fever or symptoms had very similar baseline clinical and laboratory profiles, those with fever alone tend to do worse in terms of composite end-points compared to patients with symptoms alone. Interestingly, despite the relatively higher rates of the composite study end-point, it was observed that none of the patients with fever alone (Group 3) were treated with anti-viral agents. (iv) Even though patients with symptoms alone had lower rates of the composite study end-point compared to those with fever alone, those with symptoms had higher rates of ARDS, ICU admissions and mechanical ventilation. (v) The independent predictor of the composite study end-point was the presence of fever after adjusting for important confounders. There was a trend towards worse outcomes for patients with the presence of symptoms, but this did not reach statistical significance.

The highest transmission risk is carried by individuals with asymptomatic infections or those with mild symptoms. The percentage of asymptomatic cases in case-series were 24.2%,[4] and if left undetected, remains a major source of transmission. These individuals do not seek medical attention and carry on with daily activities, while being highly contagious.[4] Our study highlights an important finding that those who had an

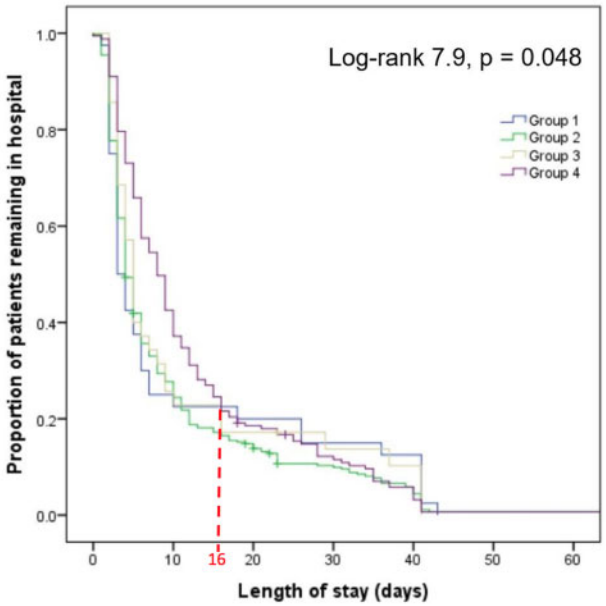

Figure 2. The proportion of COVID-19 patients remaining in hospital in relation to the length of hospital stay (in days) categorized according to the four study groups.

incidental finding of fever but remained asymptomatic, had worse clinical outcomes than those with symptoms alone. The presence of fever, even if the patient is otherwise asymptomatic, needs to be treated seriously, and should be monitored closely in an isolation facility for COVID-19 related complications. Our data suggest that these febrile patients, even in the absence of acute respiratory illness-related symptoms, may warrant early therapeutics. These patients need to be treated adequately and in a timely fashion. The safe period for monitoring these febrile patients may take up to 2 weeks as suggested by the present data.

Even though the presence of fever portends worse prognostic outcomes, careful clinical considerations are still needed for those who are symptomatic. This study found significantly higher incidence of ARDS in the symptomatic groups compared to the asymptomatic groups. This suggests that the presence of symptoms seems to be more predictive of ARDS than the presence of fever, which highlights an important reminder to all clinicians that COVID-19 patients do not need to have mounted a fever early in their presentation to be at risk of ARDS.

Stringent infectious control measures should target these young and mobile groups of people, to limit the spread of asymptomatic COVID-19 transmissions.[4,15,16] Our unique study population represents this low-risk group of young patients with a median age of 34 years, and the vast majority without comorbidities. This is contrast to the first real-world example of undocumented asymptomatic outbreak of the 'Diamond Princess' cruise ship, where although there was an increase in detection rate of COVID-19 from 14% to 69% with the implementation of compulsory COVID-19 screening swabs, their population was made up of older patients (median age of 68 years) with at least 50% of patients with comorbidities.[17] Hence, our study population is a generalizable representation of the younger population with asymptomatic infections or mild severity of the virus. Nevertheless, in comparison with the 'Diamond Princess' cruise ship cohort, those who had severe COVID-19 were generally older and had lymphopenia compared to those with mild severity of the virus; whilst the presence of fever was not found to be significantly different between the two groups.[17]

Patients with fever and symptoms tended to have increased rates of pulmonary embolism and coagulopathy. This is in keeping with the observation of increased prevalence of pulmonary embolism amongst COVID-19 patients seen in Europe.[18] The authors found that the risk factors of pulmonary embolism in COVID-19 patients were not associated with traditional thromboembolism risk factors, but rather with the clinical and biochemical profile of these patients (such as CRP and time from symptom onset), largely contributed by the degree of inflammation.[18]

In our study cohort, patients who were asymptomatic and afebrile had the lowest biochemical inflammatory response and most favourable clinical outcomes, as would be expected. They generally had lower rates of the traditional inflammatory response, such as sinus tachycardia, lymphopenia, thrombocytopenia, raised CRP, lactate dehydrogenase and ferritin. Only one patient (2.4% of the subgroup) had COVID-19 related pneumonia and AKI. These findings were in keeping with a study from China of 24 asymptomatic patients, where 16.7% had lymphopenia, but was also uncommon to have elevated CRP, D-dimer or transaminases. None of the cases developed severe pneumonia, required ICU admission or died.[19–21] Given the overall favourable clinical and biochemical profile of asymptomatic, afebrile patients, blood laboratory investigation and treatment may be of limited utility unless they turn febrile or unwell. It is indeed safe for these patients to remain outside of a healthcare facility provided that quarantine measures can be guaranteed. As with the current practice in China where asymptomatic carriers will not be investigated or treated unless they develop clinical manifestations,[22] this approach should be considered for efficient resource allocation. Low-risk, afebrile COVID-19 patients may be isolated in community isolation facilities rather than in acute hospitals. A balance needs to be struck between the testing of afebrile, asymptomatic patients to limit the effect of 'silent spreaders' through means of temperature and symptom screening in public areas, together with the rational and appropriate usage of limited medical resources (e.g. hospital bed occupancy or costs associated with basic laboratory tests).

As governments balance the re-opening of schools and workplaces, additional measures are required to further contain the outbreak.[19] Screening for fever at entrances of public areas remain an important infection control strategy. This study demonstrated that patients with fever alone, despite very similar baseline clinical and laboratory profiles, tend to have worse outcomes compared to patients with symptoms alone. The presence of fever, even in an asymptomatic COVID-19 patient, is not benign. Further prospective studies are needed to evaluate the need for early therapeutics in this subset of febrile but asymptomatic patients.

Limitations

The main strength of the study was the all-comer, real-world design, which improves the generalizability of the results to the general low-risk COVID-19 population. There were several limitations in this study. Firstly, the cross-sectional nature of a single-centre, retrospective study may result in lead-time bias as patients are recruited at different time points in their illness. However, given the mandate that all positive COVID-19 patients regardless of symptomology were admitted for assessment, this provides a real-world insight on low-risk patients with mild severity of the illness. Secondly, a portion of individuals who were identified as asymptomatic and afebrile at the index

Table 3. Independent clinical predictors of the composite study end-point

Variables	Unadjusted odds ratio	95% confidence interval	*P*-value	Adjusted odds ratio	95% confidence interval	*P*-value
Age	1.067	1.044–1.090	<0.001	1.034	0.999–1.071	0.059
Presence of fever	5.679	3.104–10.391	<0.001	4.096	1.737–9.656	0.001
Presence of symptoms	2.340	0.823–6.657	0.111	1.750	0.562–5.442	0.334
Admission pulse rate	1.010	0.996–1.025	0.167	1.004	0.985–1.023	0.696
Presence of comorbidities	5.258	2.032–8.923	<0.001	1.946	0.592–6.393	0.273
Lymphocyte count	0.277	0.167–0.458	<0.001	0.611	0.333–1.123	0.113
Ferritin	1.002	1.001–1.003	<0.001	1.000	0.999–1.017	0.719
C-reactive protein	1.022	1.013–1.031	<0.001	1.008	0.999–1.017	0.084

nasopharyngeal swab may have been pre-symptomatic, rather than truly asymptomatic, and that they may have been in the virus incubation period, only displaying symptoms at a later date after the study period.[23] Further studies with prolonged follow-up of these asymptomatic cases would be useful to assess the prevalence of 'true' asymptomatic infection.

Conclusion

In this real-world study of low-risk COVID-19 patients, the presence of fever remains an independent predictor of adverse clinical outcomes. While the presence of symptoms aids in case identification, it was not associated with adverse outcomes. Patients with fever should be monitored closely in a medical isolation facility with heightened attention to features of end-organ damage and potential clinical deterioration.

Supplementary material

Supplementary material is available at *QJMED* online.

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