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Fever Patterns, Cytokine Profiles, and Outcomes in COVID-19

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Background. Prolonged fever is associated with adverse outcomes in dengue viral infection. Similar fever patterns are observed in COVID-19 with unclear significance.

Methods. We conducted a hospital-based case–control study of patients admitted for COVID-19 with prolonged fever (fever >7 days) and saddleback fever (recurrence of fever, lasting <24 hours, after defervescence beyond day 7 of illness). Fever was defined as a temperature of ≥38.0°C. Cytokines were determined with multiplex microbead-based immunoassay for a subgroup of patients. Adverse outcomes were hypoxia, intensive care unit (ICU) admission, mechanical ventilation, and mortality.

Results. A total of 142 patients were included in the study; 12.7% (18/142) of cases had prolonged fever, and 9.9% (14/142) had saddleback fever. Those with prolonged fever had a median duration of fever (interquartile range [IQR]) of 10 (9–11) days for prolonged fever cases, while fever recurred at a median (IQR) of 10 (8–12) days for those with saddleback fever. Both prolonged (27.8% vs 0.9%; *P* < .01) and saddleback fever (14.3% vs 0.9%; *P* = .03) were associated with hypoxia compared with controls. Cases with prolonged fever were also more likely to require ICU admission compared with controls (11.1% vs 0.9%; *P* = .05). Patients with prolonged fever had higher induced protein–10 and lower interleukin-1α levels compared with those with saddleback fever at the early acute phase of disease.

Conclusions. Prolonged fever beyond 7 days from onset of illness can identify patients who may be at risk of adverse outcomes from COVID-19. Patients with saddleback fever appeared to have good outcomes regardless of the fever.

Keywords. COVID-19; cytokines; fever; prolonged; saddleback.

Since its first report in Wuhan, China, in December 2019, COVID-19 has rapidly spread, becoming a pandemic with more than 3 million confirmed cases [1]. Singapore reported its first imported case of COVID-19 in a traveler from Wuhan on January 23, 2020, followed by its first locally transmitted case on February 7, 2020 [2, 3].

COVID-19 generally presents as an acute respiratory illness, with fever, fatigue, and dry cough being commonly reported symptoms [4–6]. In particular, fever was reported in about 72%–98.6% of patients, usually lasting <7 days [4, 7–10]. However, there was a proportion of patients from our hospital who displayed 2 patterns of fever: 1 group had fever persisting into the second week of illness, while the second group displayed a saddleback pattern of fever, similar to that previously observed in dengue [11]. While it has been reported that complications of COVID-19 occur in the second week of illness, the significance of these 2 patterns of fever with regards to the development of complications is unknown [4]. A dysregulated immune response in COVID-19 has been postulated to lead a deleterious cytokine storm [12]. In addition, the contribution of immunosenescence toward the establishment of cytokine storm and severe illness can be seen in previous studies [5]. In this study, we aim to examine the characteristics of patients who developed these patterns of fever and their correlation to cytokine levels, as well as the association with adverse outcomes in COVID-19.

METHODS

Data Collection and Clinical Management

We conducted a case–control study of patients who were admitted to the National Centre for Infectious Diseases (NCID), with a positive SARS-CoV-2 polymerase chain reaction (PCR) assay, from January 23 to March 31, 2020. Upon admission, all patients underwent a chest x-ray (CXR), admission full blood count (FBC), renal and liver panel, C-reactive protein (CRP), lactate dehydrogenase (LDH), and nasopharyngeal swab for

SARS-CoV-2 PCR. Patients who tested positive were not discharged until they had 2 negative PCR tests 24 hours apart [13].

Demographic and comorbidity data, symptoms and signs, vital signs, and laboratory and radiology results were obtained from electronic medical records. A standardized template was used for recording daily signs and symptoms, vital signs, and management. The reference values for the normal ranges of laboratory tests were in accordance with those used by the hospital laboratory.

Repeat laboratory investigations and CXR were done for those with prolonged or saddleback fever and collected. For cases with prolonged fever, investigations were repeated beyond day 7 of illness, and for cases with saddleback fever, investigations were repeated at point of fever recurrence. Additional microbiological investigations, such as blood and urine cultures, influenza and respiratory viral multiplex PCR, dengue NS1 and serology, were ordered at the discretion of the primary treating clinician. The results of these microbiological investigations were also collected and analyzed.

Definitions and Outcomes

Fever was defined as a temperature of 38.0°C or higher. Duration of fever was calculated from the date of first symptom onset to the date of defervescence (defined as temperature <37.5°C for at least 24 hours) during the hospital admission. Cases with prolonged fever were defined as patients with fever lasting >7 days. Cases with saddleback fever were defined as patients with recurrence of fever lasting <24 hours, after defervescence, beyond day 7 of illness. Cases without prolonged or saddleback fever were included as controls. Cases who were already on supplemental oxygen or were already in the ICU at the time of satisfying criteria for prolonged or saddleback fever were excluded from the analysis. Hypoxia was defined as requirement for supplemental oxygen. Outcomes of interest were hypoxia, admission to the intensive care unit (ICU), need for mechanical ventilation, and mortality.

Multiplex Microbead-Based Assay for Quantification of Immune Mediators

Immune mediator levels in Triton X-100 (1%; Sigma Aldrich) inactivated plasma from a subset of patients in all 3 groups were measured using Cytokine/Chemokine/Growth Factor 45-plex Human ProcartaPlex Panel 1 (ThermoFisher Scientific), in accordance with the manufacturer's instructions. Cytokines included granulocyte-macrophage colony-stimulating factor (GM-CSF), epidermal growth factor (EGF), brain-derived neurotrophic factor, beta-nerve growth factor (bNGF), basic fibroblast growth factor (FGF-2), hepatocyte growth factor (HGF), monocyte chemoattractant protein (MCP) 1, macrophage inflammatory protein (MIP) 1α, MIP-1β, RANTES (regulated on activation, normal T cell expressed and secreted), chemokine (C-X-C motif) ligand (CXCL) 1 (GRO-α), stromal cell–derived factor 1 (SDF-1α), interferon (IFN) gamma-induced protein 10

(IP-10), eotaxin, IFN-α, IFN-γ, interleukin (IL) IL-1α, IL-1β, IL-1 receptor agonist (IL-1RA), IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12p70, IL-13, IL-15, IL-17A, IL-18, IL-21, IL-22, IL-23, IL-27, IL-31, leukemia inhibitory factor (LIF), stem cell factor (SCF), tumor necrosis factor (TNF-α), TNF-β, vascular endothelial growth factors A and D (VEGF-A, VEGF-D), platelet-derived growth factor (PDGF-BB), and placental growth factor (PLGF-1).

Statistical Analysis

Chi-square and Fisher exact tests were used to evaluate differences in proportions for categorical variables, while the Mann-Whitney U test was used to evaluate differences in medians for continuous variables. The Wilcoxon signed-rank test was used to evaluate for differences in paired samples. Statistical analyses were performed using Stata, version 14 (StataCorp, College Station, TX, USA). For cytokine profiling, the Mann-Whitney U test was applied to ascertain significant differences in immune mediator levels between patients experiencing different fever patterns. Statistical analyses were performed using GraphPad Prism, version 8. A P value of <.05 indicated statistical significance.

Patient Consent Statement

Approval for data collection by retrospective chart review with a waiver of written informed consent from study participants was granted by the Singapore Ministry of Health under the Infectious Diseases Act as part of the outbreak investigation [14]. All efforts have been undertaken to anonymize the data. Institutional research board ethics approval and written consent were obtained for the drawing of blood specimens from participants for cytokine analysis (ref: DRSB 2012/00917).

RESULTS

Demographic Profiles and Fever Patterns

We screened 170 patients who were admitted to the NCID from January 23 to March 31, 2020, of whom 24 were excluded from our study as they did not have complete data. Another 4 patients were excluded from the primary analysis as they had a saddleback pattern of fever that lasted >24 hours; 12.7% (18/142) of cases had prolonged fever and another 9.9% (14/142) had saddleback fever. Data were collected for the remaining 110 patients from this cohort as controls; 57.0% (81/142) of all study subjects were male, and the median age (interquartile range [IQR]) was 42 (31–54) years. Demographics were similar across the 3 groups (Table 1); 7.0% (10/142) of patients had comorbidities, such as diabetes (n = 4), ischemic heart disease (n = 3), and asthma (n = 3).

Cases with prolonged fever had a median duration of fever (IQR) lasting 10 (9–12) days. Higher heart rate and respiratory rate and lower oxygen saturation (spO2), systolic and diastolic blood pressure (BP) were associated with prolonged fever compared with

Table 1. Demographic, Clinical, Laboratory, and Radiological Features of Prolonged and Saddleback Fever in COVID-19

	Controls (n = 110), No. (%) or Median (IQR)	Prolonged Fever (n = 18), No. (%) or Median (IQR)	P Value	Saddleback Fever (n = 14), No. (%) or Median (IQR)	P Value
Demographics					
Male	60 (54.5)	12 (66.7)	.34	9 (64.3)	.49
Age, y	40 (30–55)	53 (42–56)	.07	44 (35–50)	.99
Vital signs					
Temperature, °C	37.3 (36.9–37.8)	38.8 (38.3–39.2)	<.01	38.3 (38.0–38.5)	<.01
Pulse, per minute	86 (75–98)	99 (89–108)	<.01	84 (80–88)	.93
Respiratory rate, per minute	18 (18–19)	21 (18–24)	<.01	20 (18–21)	.02
Oxygen saturation (SpO2), %	98 (97–99)	96 (95–97)	<.01	97 (95–97)	<.01
Systolic BP	125 (117–138)	111 (100–114)	<.01	109 (105–118)	<.01
Diastolic BP	77 (70–84)	67 (64–74)	<.01	70 (60–75)	.05
Laboratory					
White cell count, 10^9/L	4.7 (4.0–6.0)	4.9 (3.8–5.7)	.50	4.6 (3.8–4.8)	.31
Hemoglobin, g/dL	14.3 (13.2–15.1)	14.4 (13.3–14.9)	.74	14.6 (12.8–15.4)	1.00
Platelet count, 10^9/L	214 (177–263)	168 (152–213)	.04	218 (185–275)	.61
Neutrophil count, 10^9/L	2.83 (2.04–3.88)	2.80 (2.09–3.72)	.81	2.74 (1.97–3.16)	.65
Lymphocyte count, 10^9/L	1.29 (0.89–1.76)	1.045 (0.74–1.34)	.07	0.92 (0.84–1.27)	.08
ALT, U/L	25 (18–39)	33 (25–51)	.10	17 (13–32)	.28
AST, U/L	22 (17–32)	27 (24–31)	.16	22 (19–30)	.88
CRP, mg/L	4.6 (1.5–11.9)	18 (4.8–33.1)	<.01	10 (3.3–23.9)	.08
Procalcitonin, µg/L	0.04 (0.04–0.06)	0.04 (0.04–0.07)	.97	0.08 (0.04–0.15)	.26
LDH, u/L	385 (339–526)	528 (372–550)	.18	412 (346–592)	.33
Radiology					
Consolidation/infiltrates, %	27 (24.6)	6 (33.3)	.43	5 (35.7)	0.37
Progression on CXR, %		13 (72.2)	NA	5 (38.5)	NA
Outcomes					
Hypoxia, %	1 (0.9)	5 (27.8)	<.01	2 (14.3)	.03
ICU admission, %	1 (0.9)	2 (11.1)	.05	0 (0.0)	1.00
Mechanical ventilation, %	0 (0.0)	1 (5.6)	.14	0 (0.0)	1.00
Death, %	0 (0.0)	0 (0.0)	NA	0 (0.0)	NA

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BP, blood pressure; CRP, C-reactive protein; CXR, chest x-ray; ICU, intensive care unit; LDH, lactate dehydrogenase.

[a]One patient did not have a repeat CXR.

controls (Table 1). Prolonged fever was also associated with lower platelet count and higher CRP compared with controls. On repeat testing, prolonged fever was associated with a drop in hemoglobin and a rise in CRP and LDH (Table 2).

For cases with saddleback fever, fever recurred at a median (IQR) of 10 (8–12) days after symptom onset. Higher respiratory rate, lower SpO2, and lower systolic BP were also associated with saddleback fever compared with the control group. However, there were no significant differences in the admission laboratory values between the control and saddleback fever groups. There were no significant changes in laboratory findings when repeated at the point of fever, except for a rise in platelet and lymphocyte counts (Table 2).

One case with prolonged fever had concomitant infection with ventilator-associated pneumonia, with *Klebsiella pneumoniae* grown from his endotracheal aspirate on day 8 of ICU admission (day 15 of illness). None had symptoms of urinary tract infection, thrombophlebitis, or *Clostridioides difficile* diarrhea.

Outcomes

Pneumonia was present in 26.8% (38/142) of the cohort, of which 21.1% (8/38) required supplemental oxygen; 2.1% (3/142) of patients required ICU admission, 1 of whom required mechanical ventilation. There were no deaths in our study.

There was progression of infiltrates on the CXR for 72.2% (13/18) of cases with prolonged fever and 38.5% (5/13) in those with saddleback fever. Repeat CXR was not performed for cases in the control group and 1 case of saddleback fever. Cases with prolonged fever were more likely to have hypoxia (27.8% vs 0.9%; P < .01) and ICU admission (11.1% vs 0.9%; P = .05) compared with cases in the control group (Table 1). Saddleback fever was significantly associated with hypoxia (14.3% vs 0.9%; P = .03) but not ICU admission (0.9% vs 0.0 %; P = 1.00) compared with those in the control group. Both prolonged fever and saddleback fever were not significantly associated with mechanical ventilation as compared with the control group (Table 1).

The 4 cases who were excluded from the primary analysis demonstrated a saddleback pattern of fever that lasted

Table 2. Laboratory Results for Prolonged and Saddleback Fever

	On Admission, Median (IQR)	Repeat Investigations,[a] Median (IQR)	P Value (Paired)
Prolonged Fever (Paired Values Only)			
White cell count, 10^9/L	4.9 (3.8–5.7)	6.0 (4.1–6.5)	.10
Hemoglobin, g/dL	14.4 (13.3–14.9)	14.05 (12.3–14.2)	.01
Platelet count, 10^9/L	168 (152–213)	201 (169–274)	.05
Neutrophil count, 10^9/L	2.80 (2.09–3.72)	4.2 (2.52–5.19)	.03
Lymphocyte count, 10^9/L	1.05 (0.74–1.34)	0.97 (0.81–1.27)	.54
ALT, U/L	33 (25–51)	39 (27–59)	.41
AST, U/L	27 (24–31)	44 (24–57)	.18
CRP, mg/L	19.9 (4.8–33.1)	60.7 (13.4–146.4)	<.01
Procalcitonin, µg/L[b]	0.08	0.12	.32
LDH, u/L	528 (372–550)	654 (503–696)	<.01
Saddleback fever (paired values only)			
White cell count, 10^9/L	4.6 (3.95–4.95)	4.6 (4.1–5.7)	.53
Hemoglobin, g/dL	14.7 (13–15.5)	14.8 (13.4–15.2)	.58
Platelet count, 10^9/L	206 (180–270)	213 (185.5–318)	.05
Neutrophil count, 10^9/L	2.94 (2.02–3.26)	2.49 (1.99–3.84)	.75
Lymphocyte count, 10^9/L	0.92 (0.81–1.24)	1.15 (0.93–1.71)	.01
ALT, U/L	20 (16–32)	26 (17–39)	.83
AST, U/L	24 (20–29)	25 (16–31)	.17
CRP, mg/L	9.7 (3.3–15.6)	12.7 (4.7–41.2)	.23
Procalcitonin, µg/L	0.10 (0.04–0.15)	0.10 (0.04–0.15)	.65
LDH, u/L	443 (344–629)	606.5 (405–834)	.10

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BP, blood pressure; CRP, C-reactive protein; LDH, lactate dehydrogenase.

[a]Investigations were repeated at the point at which they satisfied criteria for prolonged or saddleback fever.

[b]Only 1 sample of paired values available.

>24 hours. Two remained in the general ward throughout their stay without any complications, while 2 were admitted to the ICU, 1 of whom died from acute respiratory distress syndrome.

Correlation Between Fever Patterns and Cytokine Profiles

To investigate whether the fever patterns experienced by the patients are due to differences in immune responses, concentrations of 45 immune mediators were profiled. Eleven patients with prolonged fever, 8 patients with saddleback fever and 56 patients with fever lasting ≤7 days (controls) were evaluated at the first time point of blood sample collection upon hospitalization (median of 6 days post–illness onset) (Figure 1A). Cytokine and chemokine concentrations from an additional 23 healthy controls who did not have COVID-19 were also analyzed for baseline comparison. Cases with prolonged fever were found to have higher levels of anti-inflammatory IL-1RA, pro-inflammatory IL-6, and chemokine interferon-γ IP-10 compared with controls (Figure 1B). Saddleback fever cases were also found to have higher pro-inflammatory IL-1α, T-cell-activating mediators IL-21 and IL-22, and chemokine stromal cell–derived factor 1α (SDF-1α) compared with controls (Figure 1B). Notably, patients with prolonged fever had higher IP-10 and lower IL-1α levels as compared with patients with saddleback fever (Figure 1B). The levels of other immune mediators measured were not significantly different between groups.

DISCUSSION

To our knowledge, this is the first study to examine the association between the patterns of fever and outcomes in COVID-19. While both prolonged and saddleback fever showed an association with hypoxia, only prolonged fever was associated with ICU admission. This corresponded with a rise in CRP and LDH seen in cases with prolonged fever, which are known to be associated with adverse prognostic factors in COVID-19 [15, 16]. In contrast, cases with saddleback fever showed no significant change upon repeating their laboratory tests. Despite the progression on CXR in over one-third of cases with saddleback fever, these cases tend to do well. This suggests that in patients with prolonged fever, close monitoring for deterioration should be instituted, while patients with saddleback fever who remain well and do not require supplemental oxygenation are unlikely to require close monitoring in the hospital. In addition, as these patients with saddleback fever tend to do well, there is also no need for repeat laboratory testing or CXR, as the results are unlikely to change management or clinical outcomes.

None of the 3 patients who entered the ICU had culture-proven nosocomial infections, suggesting that the fevers observed in the ICU were likely related to COVID-19 infection. Nevertheless, as patients in the ICU are at higher risk of nosocomial infections, due diligence should be done to exclude other causes of fever [17]. Physicians may consider stopping antimicrobials if all investigations are unyielding and patients remain hemodynamically stable. However, as the number of patients with prolonged fever requiring ICU admission is small in this cohort, further studies should be done to prove this correlation.

The differences in cytokine and chemokine profiles among control patients with fever ≤7 days, patients with prolonged fever, or patients with saddleback fever at the early acute phase of illness suggest that different immunological responses could result in the differences in the clinical phenotype observed. Although there were no significant differences in white blood cell counts or absolute values of lymphocytes and CRP, we found significant differences in plasma IL-6 and IP-10 levels between the prolonged fever and control patients. In addition to their pro-inflammatory properties, both IL-6 and IP-10 have been reported to be associated with disease severity and ICU admission in COVID-19 [18, 19] . In addition, IP-10 has also been reported to be associated with increased viral load, lung injury, ICU admission, and mortality [21]. This corroborated well with our findings of increased hypoxia in patients with prolonged fever.
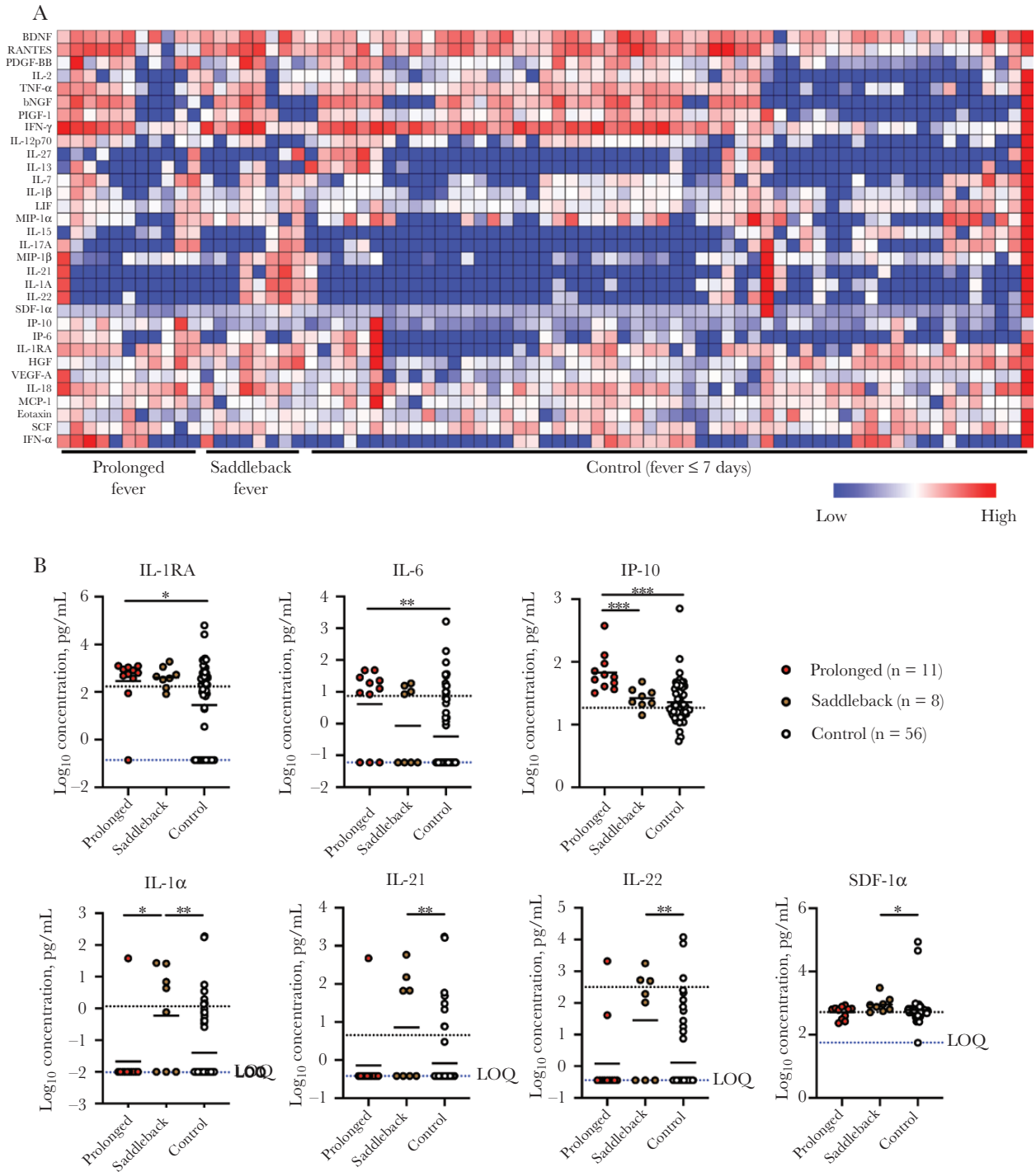
Figure 1. Plasma immune mediator levels in COVID-19 patients experiencing different fever patterns. Plasma fractions were isolated from blood samples of COVID-19 patients collected during the acute phase (median post-illness onset, 6 days). Concentrations of 45 immune mediators in plasma were quantified using a 45-plex microbead-based immunoassay. A, Heatmap showing the relative concentration of cytokines across patients with different fever patterns. Blue and red represent low and high concentrations, respectively. B, Comparison of immune mediator levels in patients with prolonged fever (n = 11), patients with saddleback fever (n = 8), and patients with fever that lasted ≤7 days (control; n = 56). Statistical analyses were performed with the Mann-Whitney U test (*P < .05; **P < .01; ***P < .001). Cytokine level for healthy controls (n = 23) is indicated by the black dotted line. Patient samples that are not detectable are presented as the value of logarithm transformation of limit of quantification (LOQ), indicated by the blue dotted line.

Interestingly, there are also higher plasma levels of IL-1RA in patients with prolonged fever compared with control patients. Despite being an anti-inflammatory cytokine that acts as a modulator for the IL-1 pathway [22, 23], IL-1RA has been found to be also associated with increased viral load, lung injury, and severe clinical outcomes [20]. IL-1RA is naturally secreted by human hosts to limit the activity of IL-1 during hyperinflammation [22]. The elevation of circulating IL-1RA may reflect overactive IL-1 activation, which has been reported to associated with severe outcomes in COVID-19 [24].

In patients with saddleback fever, higher levels of IL-1α, IL-21, IL-22, and SDF-1α were observed compared with control patients. IL-1α is a pyrogenic cytokine that plays a central role in inflammatory diseases like arthralgia [23]. The higher levels of IL-1α could initiate the first occurrence of fever, while the pro-inflammatory cytokines IL-21 and IL-22 mediate the activation of T cells and M1 macrophages [25, 26], which drive the recurrence of fever in saddleback fever cases. At the time of writing, there were no supporting studies on the association between elevated levels of IL-21, IL-22, and SDF-1α and COVID-19.

Comparing the difference between prolonged fever cases and saddleback fever cases, we found an increased IL-1α level and lower IP-10 level on admission. A lower IP-10 level is consistent with the finding that saddleback fever cases tend to have better clinical outcomes than prolonged fever cases. This phenomenon is also observed in other viral fevers, like dengue virus [27] and thrombocytopenia syndrome virus [28, 29], where patients with more severe illness have higher serum levels of IP-10. However, it is interesting that there are higher pro-inflammatory IL-1α levels in patients with saddleback fever. IL-1α is dual function cytokine that can act as both a transcription factor and a damage-associated molecular pattern (DAMP), which can be released by necrotic cells to promote and exacerbate inflammation via IL-1R1 [30]. In hypoxic conditions, it can trigger the expression of chemokines that attract neutrophils and monocytes to the ischemic tissue [31]. Importantly, upregulation of the IL-1 pathway on monocytes can increase prostaglandin E2 expression and drive fever [32]. Notably, in a study of 3 COVID-19 patients, peak IL-1α appeared to precede the nadir of lung function [33], which may herald worsening inflammation. This apparent difference in IL-1α between prolonged fever cases and saddleback fever cases may have occurred due to dynamic immune response and the time point of sample collection. Patients with prolonged fever may have had higher levels of IL-1α earlier on before sample collection.

The results of this study can be used to optimize placement of patients with COVID-19. Home or community isolation facilities and the other iterations for positive cases are commonly used globally to isolate positive patients [34, 35]. Such facilities free up hospital beds to enable sicker patients to be optimally managed. Teleconferencing is often used to monitor these cases for potential deterioration. Self-recorded temperature monitoring for COVID-19 patients at home or community isolation facilities can be used to triage patients who need admission to the hospital. In addition, in comparison with other parameters such as respiratory rate, heart rate, or blood pressure, fever is easy to detect and readily identifiable as a risk factor for severe disease. Based on this study, patients with saddleback fever who remain well can be monitored in the community, while patients who have fever for >7 days should be admitted for closer monitoring.

One limitation of the study is the small sample size of our cohort. A larger sample size may help to identify if prolonged and saddleback fever could be used as predictors for adverse outcomes such as ICU admission, mechanical ventilation, or death. Our cohort only had 1 mortality, and this may be reflective of the overall low mortality rate in Singapore. At the time of writing, the mortality rate from COVID-19 in Singapore was 0.09% [36]. Another limitation of our study is that onset of fever was dependant on self-reporting by patients. Over- or under-reporting of the onset of fever before admission could affect the number of patients found to have prolonged or saddleback fever. We also excluded 4 patients whose fever pattern did not fulfill the case definition for prolonged or saddleback fever. Two of these patients were admitted to the ICU, which may suggest another phenotype of patients who are at higher risk of adverse outcomes. A larger cohort might help to improve our understanding of these patients.

In conclusion, we reported on the prevalence, risk factors, cytokine profiles, and outcomes of patients with COVID-19 who had saddleback or prolonged fever. Patients with prolonged fever are more likely to develop hypoxia and have a more pronounced inflammatory response in comparison with those in the saddleback fever group, which is also reflected in the different cytokine profiles between the 2 groups. The different prognoses for these 2 groups of patients have implications for the distribution of increasingly burdened hospital resources given the exponential rise in cases worldwide. More studies are required to validate the findings of this report.

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