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Viral arthralgia a new manifestation of COVID-19 infection? A cohort study of COVID-19-associated musculoskeletal symptoms

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ABSTRACT

Objectives: Musculoskeletal symptoms are often unrecognised as a prominent feature of COVID-19 infection. This study hypothesised that viral arthralgia is an uncommon but distinct manifestation of COVID-19 infection. In addition, it aimed to characterise the other musculoskeletal presentations of COVID-19 infection and study their prognostic implications.
Methods: Patients hospitalised with COVID-19 infection were divided into two groups: those with and without musculoskeletal symptoms. Those with musculoskeletal symptoms were subdivided according to four patterns of musculoskeletal involvement: myalgia, arthralgia, backache and generalised body ache. Using binary regression logistic analysis, the risk of developing a viral pneumonia in patients with and without musculoskeletal complaints was compared.
Results: Of 294 hospitalised patients with COVID-19, 88 (30%) reported musculoskeletal complaints. Among these 88 patients, 37.5% had myalgia, 5.7% arthralgia, 6.8% new-onset backache and 50% generalised body ache. The presence of musculoskeletal complaints was not associated with the risk of developing viral pneumonia (6.8% vs. 9.7%, OR 0.68, 95% CI 0.26–1.76, $p = 0.426$). COVID-19 arthralgia was often more severe and had variable onset, while generalised body ache and myalgia were milder and coincided with the occurrence of fever or respiratory symptoms.
Conclusion: Viral arthralgia is a novel clinical manifestation of COVID-19, and untypical of a viral prodrome or a reactive arthropathy. While musculoskeletal symptoms were not associated with developing a pneumonia, to avoid missing a diagnosis of COVID-19, clinicians should be aware of its variable onset, particularly when respiratory symptoms are absent at the time of presentation.

Introduction

Singapore was one of the first countries to report its index case of COVID-19 on 23 January 2020 (Chotirmall et al., 2020). Since then, it has been one of the most successful in limiting community spread by extensive testing, meticulous contact tracing, active screening of at-risk groups, pre-emptive hospitalisation and mandatory mask-wearing (Chotirmall et al., 2020). As a result, hospitals have remained well-equipped and mortality rates from COVID-19 remain one of the lowest globally (Worldometers, 2020). The vast majority of patients with COVID-19 admitted to hospitals in Singapore remain clinically well; however, musculoskeletal symptoms have been noticed to be a prominent complaint among them. Particularly interesting is a small subgroup of patients who present with a viral arthralgia, which may be an uncommon but currently under-recognised new clinical entity in COVID-19 (Gupta et al., 2020a; Zheng et al., 2020).

COVID-19 is a global pandemic that predominantly affects the respiratory tract but also has multiorgan involvement. Musculoskeletal complaints have been described in 15–36% of cases (Li et al., 2020; Guan et al., 2020), but characterisation of their clinical features and implications are currently limited. Myalgia may be frequently observed in viral infections and represents a cytokine response (Kelvin et al., 2011; Bian et al., 2014); however, viral-associated arthralgias and acute arthritis are less commonly seen in acute respiratory viral infections (Tiwari and Bergman, 2020). Among patients with arthritis, 1.5% had a viral aetiology detected (Varache et al., 2011). Viral arthralgia has been described to occur in parvovirus B19, hepatitis B virus, human immunodeficiency

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virus (HIV), flaviviruses and alphaviruses (Marks and Marks, 2016; Oliveira and Silva, 2019), but is an uncommon complaint in COVID-19. Given that immune dysregulation and complement activation can occur in COVID-19 infection (Gupta et al., 2020b; Azkur et al., 2020), this may lead to immune complex deposition within joints or transient synovitis, which have been reported in other viral infections (Wands et al., 1975; Goupil and Mores, 2016).

Viral arthralgia in COVID-19 has been described in isolated case reports (Parisi et al., 2020; Liew et al., 2020; Joob and Wiwanitkit, 2020), but their significance as a new clinical entity has not been fully appreciated. Interestingly, they have been reported to occur independently of respiratory symptoms in COVID-19. One case in Italy occurred as a reactive arthritis 25 days after the onset of acute respiratory symptoms (Parisi et al., 2020). A second case of reactive arthritis diagnosed with COVID-19 from active screening was completely asymptomatic for respiratory symptoms (Liew et al., 2020), and a third case in Thailand presented with fever and arthralgia, which pre- dated the onset of respiratory symptoms (Joob and Wiwanitkit, 2020), leading to a delayed diagnosis of COVID-19 infection. Without a high clinical index of suspicion and adequate follow-up, the diagnosis may be easily missed if there is an overemphasis on respiratory symptoms.

A descriptive cohort study was undertaken of hospitalised patients with COVID-19 infection, diagnosed by reverse transcription polymerase chain reaction (RT-PCR), admitted to the general wards of Woodlands Health Campus in Singapore. The aim of this study was to characterise the prevalence, onset and nature of musculoskeletal complaints in COVID-19 patients and their clinical significance. It was hypothesised that viral arthralgia is an uncommon but distinct manifestation of COVID-19 infection, which could present days before or after the onset of respiratory symptoms. In addition, it was hypothesised that musculoskeletal symptoms are not associated with the development of a viral pneumonia.

Methods

Subjects and study design

A single-centre retrospective cohort study was conducted of patients at Woodlands Health Campus Singapore between 1 April

Table 1
Clinical characteristics according to presence of musculoskeletal symptoms.

Characteristic	Reference range	All patients (N = 294)	With MSK symptoms (N = 88)	Without MSK symptoms (N = 206)
Demographics				
Age, years		36 (30, 45)	35 (30, 43)	37 (30, 46)
Male		294/294 (100)	88/88 (100)	206/206 (100)
Nationality*				
Bangladeshi		165/293 (56)	59/88 (67)	106/205 (52)
Indian		83/293 (28)	23/88 (26)	60/205 (29)
Chinese		30/293 (10)	4/88 (5)	26/205 (13)
Others		15/293 (5)	2/88 (2)	13/205 (6)
Symptoms				
Any MSK symptom		88/294 (30)	88/88 (100)	0/206 (0)
Generalised body ache		44/294 (15)	44/88 (50)	0/206 (0)
Arthralgia		5/294 (2)	5/88 (6)	0/206 (0)
Myalgia only		33/294 (11)	33/88 (38)	0/206 (0)
Backache		6/294 (2)	6/88 (7)	0/206 (0)
Fever*		219/294 (74)	84/88 (96)	134/206 (65)
Respiratory Sx		206/294 (70)	65/88 (74)	141/206 (68)
Fever without respiratory Sx		57 (19)	22/88 (25)	35/206 (17)
Neither fever nor respiratory Sx*		31/294 (10)	1/88 (1)	30/206 (15)
Comorbidities				
Any		41/294 (14)	12/88 (14)	29/206 (14)
Diabetes		26/294 (9)	8/88 (9)	18/206 (9)
Hypertension		13/294 (4)	6/88 (7)	7/206 (3)
Coronary artery disease		2/294 (1)	0/88 (0)	2/206 (1)
Chronic renal disease		0/294 (0)	0/88 (0)	0/206 (0)
Chronic lung disease		1/294 (0)	1/88 (1)	0/206 (0)
Laboratory findings				
CRP*, mg/l	1.0–5.0	3.1 (1.2, 7.9)	4.2 (1.9, 8.2)	2.5 (1, 7.1)
LDH, U/l	134–264	185 (166, 200)	190 (166, 215)	186 (165, 210)
TW, $\times 10^9$/l	3.82–9.91	6.4 (5.2, 7.7)	6.3 (5.2, 7.5)	6.4 (5.3, 7.8)
Lymphocytes, $\times 10^9$/l	1.13–3.49	1.7 (1.3, 2.2)	1.7 (1.3, 2.3)	1.7 (1.3, 2.2)
Neutrophils, $\times 10^9$/l	1.87–6.50	3.6 (2.6, 4.8)	3.3 (2.3, 4.7)	3.7 (2.8, 4.9)
N/L ratio	–	2 (1.4, 3.2)	1.8 (1.2, 3.1)	2.1 (1.5, 3.3)
Platelets, $\times 10^9$/l	173–414	223 (186, 263)	213 (177, 252)	227 (192, 270)
Tested for dengue co-infection		35/294 (12)	14/88 (16)	21/206 (10)
Outcome				
Pneumonia		26/294 (9)	6/88 (7)	20/206 (10)
Length of stay, days		3 (2,4)	3 (2,5)	3 (2,4)
O2 requirement		1/294 (0)	1/88 (1)	0/206 (0)
ICU		1/294 (0)	1/88 (1)	0/206 (0)
Mortality		0/292 (0)	0/88 (0)	0/206 (0)

Data are represented as median (interquartile range) for continuous or nominal data, and number (%) for categorical data.
Abbreviations: MSK = musculoskeletal; Sx = symptoms; CRP = C- reactive protein; LDH = lactate dehydrogenase; TW = total white cell count; N/L=neutrophil/lymphocyte; ICU = intensive care unit; NR = not reported.
* $p < 0.05$ between groups with and without MSK symptoms.

and 31 May 2020. Subjects were included if they were aged ≥18 years, of general ward status at the time of admission and diagnosed with COVID-19 via RT-PCR from nasopharyngeal or throat swab specimens. This study was approved by the Institution Ethics Board (DSRB 2020/00765) and strict patient confidentiality was maintained.

Exclusion criteria included pregnant patients, those with severe debilitating end-stage disease on palliative care, those with missing documentation of the onset and nature of presenting symptoms, missing information on the outcome of developing a pneumonia, or those who were still hospitalised at the end of data collection because the endpoint of developing pneumonia was unknown. At the time of completion of data collection on 31 July 2020, all patients had been discharged. No subject was excluded based on any of the above criteria.

Classification and definitions

Musculoskeletal complaints were considered to be related to COVID-19 infection if they were of new onset within 2 weeks prior or 1 month after the diagnosis of COVID-19 infection. Pain localising to the chest, abdomen or headaches were not considered musculoskeletal in nature. Subdivision into groups of myalgia, arthralgia, backache, or generalised body aches were determined by localisation to the muscle, joint(s), back or unspecified, respectively, as documented in the detailed history in the case notes. If there were two or more types of musculoskeletal symptoms, patients were classified according to their predominant complaint.

Data collection

Data were obtained from electronic health records. Information was collected on: patient demographics; comorbidities; history of presenting complaint, including pain score, duration of pain, onset and distribution, development of fever or respiratory symptoms, clinical examination, use of analgesia, length of stay; and COVID-19-related biochemical characteristics on admission, including C-reactive protein (CRP), lactate dehydrogenase (LDH), total white cell count (TW), lymphocyte, neutrophil and platelet counts and dengue serology for the presence of co-infection. Pain score was taken to be the maximum recorded on the first 72 h of admission, as assessed by a visual analogue scale from 0 to 10. Daily case notes were inspected to the day of discharge, particularly looking for new-onset musculoskeletal symptoms, clinical and radiological evidence of pneumonia that developed during the admission. Two doctors (CWSH and MNMEA) extracted all the pre- defined variables, and the data were cross-checked for integrity before analysis. Where there were different interpretations, these were resolved by mutual consensus and adjudication by the principal investigator (LJE).

Outcomes

The study was primarily descriptive to highlight a new clinical entity. The outcomes that were analysed were the development of pneumonia, as determined radiologically and clinically, and requirement for supplemental oxygen and intensive care unit (ICU) care, and mortality as documented in case sheets. The

Table 2
Characteristics and outcome of patients with musculoskeletal complaints.

	Reference range	Generalised body ache (N = 44)	Arthralgia (N = 5)	Myalgia (N = 33)	Backache (N = 6)
Age, years		34 (31, 42)	44 (38, 45)	36 (29, 43)	31 (29, 42)
MSK symptoms					
Day of MSK Sx onset in relation to fever or respiratory Sx		0 (0, 0)	0 (−1, 6)	0 (0, 0)	2 (0, 6.3)*
Duration of MSK Sx		3 (2, 4)	9 (7, 18)**	3 (2, 4)	1.5 (1, 5)
Pain score on admission		0 (0, 0)	2 (0, 5)	0 (0, 2)	0 (0, 1)
Types of analgesia required		1 (1, 1)	3 (2,3)***	1 (1, 1)	1 (1, 2)
Associated symptoms					
Fever		41/44 (93)	4/5 (80)	33/33 (100)	6/6 (100)
Respiratory Sx		35/44 (80)	5/5 (100)	20/33 (61)	5/6 (83)
Fever without respiratory Sx		8/44 (18)	0/5 (0)	13/33 (39)	1/6 (17)
Neither fever nor respiratory Sx		1/44 (2)	0/5 (0)	0/33 (0)	0/6 (0)
Laboratory findings					
CRP, mg/l	1.0–5.0	3.6 (1.5, 8.3)	2.7 (1, 5.8)	4.7 (2, 9.7)	4.0 (3.4, 5.6)
LDH, U/l	134–264	188 (160, 219)	214 (190, 215)	184 (166, 201)	192 (188, 197)
TW, $\times 10^9$/l	3.82–9.91	6.7 (5.1, 7.7)	6.7 (6.3, 7.1)	6 (5.2, 7)	5.7 (4.7, 7.1)
Lymphocytes, $\times 10^9$/l	1.13–3.49	1.8 (1.3, 2.5)	2 (1, 2.6)	1.5 (1, 1.8)	1.8 (1.5, 2.2)
Neutrophils, $\times 10^9$/l	1.87–6.50	3.2 (2.2, 4.8)	3.6 (3.6, 4.4)	3.3 (2.5, 4.9)	2.8 (1.9, 4)
N/L ratio	–	1.7 (1.2, 3)	1.8 (1.3, 4.6)	2.2 (1.2, 3.5)	1.5 (1.2, 1.8)
Platelets, $\times 10^9$/l	173–414	216 (177, 260)	241 (204, 262)	199 (172, 231)	239 (231, 252)
Outcome					
Pneumonia		4/44 (9)	0/5 (0)	1/33 (3)	1/6 (17)
Length of stay, days		3 (2, 5.3)	4 (3, 5)	3 (2, 5)	4.5 (3.3, 6.5)
O2 requirement		1/44 (2)	0/5 (0)	0/33 (0)	0/6 (0)
ICU		1/44 (2)	0/5 (0)	0/33 (0)	0/6 (0)
Mortality		0/44 (0)	0/5 (0)	0/33 (0)	0/6 (0)

Data are represented as median (interquartile range) for continuous or nominal data, and number (%) for categorical data.
Abbreviations: MSK = musculoskeletal; Sx = symptoms; CRP = C- reactive protein; LDH = lactate dehydrogenase; TW = total white cell count; N/L = neutrophil/lymphocyte; ICU = intensive care unit.
* $p < 0.05$ on ANOVA: post-hoc test significant between backache, generalised body ache and myalgia groups.
** $p < 0.05$ on ANOVA: post-hoc test significant between arthralgia and backache groups.
*** $p < 0.05$ on ANOVA: post-hoc test significant between arthralgia and all other groups.

requirement for supplemental oxygen was defined as finger oxygen saturation ≤93% on room air, or arterial blood oxygen partial pressure (PaO_2)/oxygen concentration (FiO_2) ≤300 mmHg.

Statistical analysis

Statistics were performed using SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, New York). Continuous variables were presented as mean ± SD or median (interquartile range), and categorical data were shown as n (%). Clinical characteristics were compared between patients with and without musculoskeletal symptoms, and between patients in the different musculoskeletal groups using the Mann–Whitney U test, Fisher's exact test and one-way ANOVA, as appropriate. Binary logistic regression analysis was used to identify factors associated with the development of pneumonia. Considering that the number developing pneumonia was small, this model included the limited covariates of age, diabetes, hypertension and presence of musculoskeletal symptoms, fever, and respiratory symptoms to avoid overfitting. A two-tailed p-value of <0.05 was considered statistically significant.

Results

Population characteristics

A total of 294 patients were hospitalised for COVID-19 infection (Table 1). The median age was 36 years (IQR 30–45) and all were male. The young age and overwhelming predominance of males among COVID-19 infections was due to the disease outbreak in foreign worker dormitories and a low community transmission rate in Singapore (Ministry of Health Singapore, 2020a). Musculoskeletal complaints were reported in 30% of the cohort. Of the 88 patients with musculoskeletal symptoms, 37.5% had myalgia, 5.7% arthralgia, 6.8% new-onset backache and 50% generalised body ache. Patients with arthralgia were non- significantly older than those without arthralgia (median age 44 vs. 36 years, p = 0.078). One patient in this cohort had a history of rheumatological disease (gout), but he did not develop musculoskeletal symptoms during this hospitalisation.

Comparing patients with and without musculoskeletal symptoms, age and comorbidities were similar in both groups (Table 1). Patients with musculoskeletal symptoms had a higher prevalence of fever ($p < 0.01$) and a higher CRP level ($p < 0.01$). Respiratory symptoms were similar in both groups without and without musculoskeletal symptoms. LDH, platelet count, TW, lymphocyte, neutrophil count and neutrophil-lymphocyte ratio were not significantly different. CRP was significantly higher in patients with musculoskeletal symptoms compared to without musculoskeletal symptoms, but levels were similar among the four groups of patients with various musculoskeletal symptoms. LDH, a marker of inflammation as well as tissue damage, was similar across all four musculoskeletal symptom groups.

Characterisation of musculoskeletal symptoms

Patients with myalgia, backache or generalised body ache experienced only mild pain on admission, with a median maximum pain score of 0 (IQR 0, 2), 0 (IQR 0, 1), 0 (IQR 0, 0) (Table 2) out of 10. In contrast, those with arthralgia reported a higher median pain score of 2 out of 10 (IQR 0, 5) on admission and required more analgesia than all other groups. The majority of patients in all groups experienced fever and/or respiratory symptoms; 25% of subjects with musculoskeletal symptoms experienced fever without respiratory symptoms. While the onset of the generalised body ache or myalgia coincided with the onset of fever or respiratory symptoms, arthralgia could occur before, during or after the onset of fever or respiratory symptoms (range 12 days before to 6 days after), and backache occurred more than 2 days (range 0–13) later. Musculoskeletal symptoms were more persistent in the arthralgia group, lasting a median of 9 days (IQR 7, 18) as compared to 3 days (IQR 2, 4), 3 days (IQR 2, 4) and 1.5 days (IQR 1, 5) in the other groups with generalised body ache, myalgia and backache, respectively.

The distribution of joint involvement was unique in each of the five patients who had a viral arthralgia (Table 3). Two patients had an oligoarthropathy, one had a monoarthropathy affecting the shoulder and two had a polyarthropathy. Three patients had only large joint involvement in the knees, shoulders and elbows, one only small joint involvement in the proximal interphalangeal joint (PIPJ) and metacarpophalangeal joints (MCPJ) of the hand, and one had both large and small joint involvement. The affected joints were symmetrically distributed in three patients and unilateral in two patients. None of the five patients had joint swelling, effusion or evidence of synovial inflammation on clinical examination;

Table 3
Clinical features of five patients with acute arthralgia.

Case	Age/ gender	Arthralgia onset wrt fever or respiratory Sx	PMH	Involved joints	Tendonitis present?	Joint effusion present?	Max pain score in first 72 h	Analgesia required in index admission	Duration arthralgia lasted	COVID-19 outcome
1	53/M	−1 day	T2DM	Small joint of hands, bilateral wrists, elbows, shoulders, SC joints, knees, ankles, upper thoracic spine	No	No	7/10	Paracetamol with orphenadrine, tramadol, topical lignocaine	29 days	No pneumonia, discharged well
2	38/M	−12 day	Nil	Bilateral elbows and knees	Yes: over extensors of bilateral elbows	No	2/10	Paracetamol, topical ketoprofen	18 days	No pneumonia, discharged well
3	38/M	+6 day	Nil	Left middle finger PIPJ and MCPJ	No	No	0/10	Paracetamol with orphenadrine, tramadol, etoricoxib	At least 7 days (discharged with arthralgia)	No pneumonia, discharged well
4	45/M	0 day	Nil	Bilateral knees, right shoulder	No	No	0/10	Paracetamol, topical ketoprofen	2 days	No pneumonia, discharged well
5	44/M	+6 day	Nil	Left shoulder	No	No	5/10	Paracetamol, tramadol, topical ketoprofen	9 days	No pneumonia, discharged well

Abbreviations: Sx = symptoms; wrt = with respect to; PMH = past medical history; SC = sternoclavicular; PIPJ = proximal interphalangeal joint; MCPJ = metacarpal-phalangeal joints.

none had an associated rash, enteritis, conjunctivitis or urethritis. In addition, one patient (Patient 3) had evidence of tendonitis over the extensor tendons of both elbows. Patient 1 tested negative for *Gonococcal* and *Chlamydia trachomatis* PCR from urethral swab, and was negative for rheumatoid factor (data not shown). None of the five patients with arthralgia had a past history of osteoarthritis, gout or an alternate rheumatic disease. Of patients with arthralgia, 80% experienced persistent pain lasting more than 1 week, and patient 1 experienced a protracted polyarthralgia lasting 29 days (Table 3).

Testing for dengue co-infection

Given the overlap in clinical features of fever, aches, leucopoenia and thrombocytopenia also observed with dengue fever, which is endemic in Singapore (Ministry of Health Singapore, 2020b), dengue IgG, IgM and NS1 antigen were evaluated in 35 patients. All 35 patients were found to be negative for dengue co-infection. As expected, those who were tested for dengue co-infection by the primary physician had clinical features overlapping with dengue fever, in particular they had lower platelet levels, more pronounced lymphopenia and a higher prevalence of fever than those who were not tested for dengue (Supplementary Table 1). Co-infection with other vector-borne diseases such as chikungunya fever and zika virus was not tested for, as these are rare in Singapore (Ministry of Health Singapore, 2020b).

Musculoskeletal symptoms are not associated with adverse outcome

In the entire cohort, 9% developed a pneumonia (Table 1). None required supplemental oxygen and all were discharged in good health. There was no difference in the likelihood of developing pneumonia in patients with and without musculoskeletal complaints (6.8% vs. 9.7%, OR 0.68, 95% CI 0.26–1.76, $p = 0.426$), despite a higher CRP level in the group of patients with musculoskeletal symptoms (Table 1). On binary logistic regression, diabetes was associated with an increased risk of developing a pneumonia (OR 3.5, 95% CI 1.2−10.1, $p = 0.019$) (Table 4), while the presence or absence of musculoskeletal symptoms was not a significant predictor of the risk of developing a pneumonia (OR 0.84, 95% CI 0.29–2.43, $p = 0.75$). There was no between-group difference in outcome of developing a pneumonia for patients with musculoskeletal presentations. The outcome of COVID-19 infection was favourable for these five patients with arthralgia and none developed a pneumonia.

Discussion

To date, studies in COVID-19 have considered the occurrence of myalgias and arthralgias together as a single entity (Cipollaro et al., 2020). This is the first study to characterise the various musculoskeletal presentations of COVID-19 and highlight COVID-19-associated arthralgia as a new manifestation previously under-recognised by clinicians (Gupta et al., 2020a; Zheng et al., 2020).

Table 4
Binary logistic regression of clinical factors and risk of developing pneumonia.

Variable	β	*p*-Value	Odds ratio (95% CI)
Age	0.013	0.6	1.01 (0.97−1.06)
MSK Sx	−0.17	0.75	0.84 (0.29−2.43)
Fever	−0.78	0.1	0.46 (0.18−1.17)
Respiratory Sx	0.23	0.64	1.26 (0.49−3.24)
Diabetes mellitus	1.3	0.019	3.5 (1.2−10.1)
Hypertension	0.43	0.62	1.53 (0.29−2.43)

Abbreviations: MSK = musculoskeletal; Sx = symptoms.

Musculoskeletal complaints are commonly seen in viral infections (Franssila and Hedman, 2006). The prevalence of 30% in this cohort of COVID-19 patients is consistent with that reported in other studies (Li et al., 2020; Guan et al., 2020; Chen et al., 2020). Viral arthralgia is less commonly seen than myalgia in COVID-19, but has also been described in other coronavirus infections (Friedman et al., 2018; Li et al., 2006; Memish et al., 2020). Its low prevalence of 2% among patients infected with COVID-19 in this study is similar to that observed in other forms of viral arthralgia (Varache et al., 2011). The current study confirms and unifies the observations from recent case reports (Parisi et al., 2020; Liew et al., 2020; Joob and Wiwanitkit, 2020).

A related case series of four patients reported acute inflammatory arthritis to be associated with COVID-19 (López-González et al., 2020). However, all had a previous history of gout or recurrent arthritis, and all demonstrated the presence of monosodium urate or calcium pyrophosphate, confounding the diagnosis of a viral-associated reactive arthralgia. In contrast, the current patients with acute arthralgia were younger, none had a history of prior arthritic attacks and they did not have clinical evidence of inflammatory joint effusions. This made the diagnosis of gout or pseudogout flare less likely. This is the first cohort study that specifically describes the arthralgia in COVID-19 patients to be distinct from other musculoskeletal manifestations and not be attributable to other causes of acute inflammatory arthritis, suggesting this to be a novel clinical manifestation of COVID-19. Dengue co-infection was also unlikely to account for the musculoskeletal symptoms in this cohort.

COVID-related arthralgia appears to be a distinct clinical entity from the generalised body ache and myalgia that are more commonly described, because it does not conform to the classical prodromal symptoms of a viral infection. Although numbers are small, this group appeared to be older, symptoms were more protracted, and the onset of arthralgia sometimes occurred days before or after the onset of fever and respiratory symptoms. In contrast, myalgia has been reported to coincide with the occurrence of viral illnesses, which is thought to be a result of the acute cytokine response and often resolves after resolution of fever (Kelvin et al., 2011; Bian et al., 2014). In the current study, patients with arthralgia also had more severe pain and required more analgesia than those with other types of musculoskeletal complaints. In two separate case reports of COVID-19-associated reactive arthritis, one occurred 3 days after and another occurred 20 days after the onset of fever or respiratory symptoms (Liew et al., 2020; Saricaoglu et al., 2020). A tendency towards an older age has also been observed in other case reports describing COVID-19- associated arthralgia (Liew et al., 2020; López- González et al., 2020; Saricaoglu et al., 2020). Arthralgia was observed to last for more than a week in most of the current patients, contributing to recent literature about an emerging syndrome of post-acute COVID-19, also known as 'long Covid', where symptoms can persist long after the recovery of a relatively mild COVID-19 infection (Greenhalgh et al., 2020; Mahase, 2020). These cases of arthralgia were not attributable to a reactive arthritis, given that the distribution of joint involvement in this cohort was not typical of the predominantly lower limb involvement seen in reactive arthritis, and there was no evidence of urethritis or enteritis, as stated in the criteria written by (Selmi and Gershwin (2014).

Mechanisms for arthralgia in COVID-19 are currently unknown. Angiotensin- converting enzyme 2, known to be a receptor for entry of SARS-CoV2 into cells, is expressed in multiple extrapulmonary tissue (Hamming et al., 2004). Direct viral synovial damage is a plausible mechanism for arthralgia, given that ACE-2 was also found to be present in synovial tissue (Mokuda et al., 2020). However, there have been no previous studies demonstrating the presence of SARS-CoV-2 in synovial tissue. In two case

reports of COVID-19-related reactive arthritis, SARS-CoV-2 was not detected within the synovial fluid (Liew et al., 2020; Ono et al., 2020). Immune complex deposition is involved in the pathogenesis of viral arthritis seen in hepatitis B and parvovirus (Wands et al., 1975; Kerr, 2000), and has been proposed to contribute to the inflammatory cascade in SARS-CoV-2 infection, although no one has studied its presence in synovial fluid in COVID-19 infection. Transient synovitis or enthesopathy are other possible mechanisms implicated in viral-associated arthralgia (Goupil and Mores, 2016; Whitelaw and Varacallo, 2020). Given the possibility for more than one pathogenic mechanism behind COVID-associated viral arthralgia, the onset has been variably observed to occur days before or after the onset of fever or respiratory symptoms.

As there has been a substantial proportion of COVID-19 patients with musculoskeletal symptoms, and a quarter of those with musculoskeletal symptoms had fever without concurrent respiratory symptoms, COVID-19 has to be considered as a differential in equatorial countries, where vector-borne diseases such as dengue or chikungunya are endemic. In the case report by Joob, a Thai lady who presented with fever and arthralgia prior to developing respiratory symptoms was initially misdiagnosed as having dengue fever (Joob and Wiwanitkit, 2020). This study highlights the importance of recognising musculoskeletal symptoms as a prominent presenting complaint of COVID-19 infection, in order to diagnose and institute appropriate isolation measures in a timely fashion.

The results of this study confirm the hypothesis that the presence of musculoskeletal symptoms was not predictive of the risk of developing a pneumonia, which is consistent with that observed in another study (Lippi et al., 2020). This is despite a higher prevalence of fever and CRP, which is a biomarker of inflammation. In addition, none of the patients with arthralgia developed a pneumonia; however, the numbers were too small in this group to make a definite conclusion. Larger studies are required to investigate if the presence of arthralgia or musculoskeletal symptoms may indicate a favourable prognosis. This analysis did demonstrate diabetes to be correlated with an increased risk of developing COVID-19 pneumonia, which are findings echoed by reports from other centres worldwide (Zhou et al., 2020).

There were some limitations to this study. First, all patients were relatively young and healthy adult males, due to the foreign worker predominance of the outbreak of COVID-19 infections in Singapore. The study was conducted on patients admitted to the general ward, excluding those who presented with severe manifestations of COVID-19. Hence, these factors may have limited the generalisability to other populations. Second, statistical analysis was limited by the low number of patients who developed adverse COVID-19 events, which is reflective of Singapore's national statistics as one of the world's lowest mortality rates for COVID-19 infection (Worldometers, 2020). This may have been partly attributable to a milder strain of the virus in Singapore (Young et al., 2020), hence the findings may not be applicable to other cohorts worldwide. Third, as most patients had mild musculoskeletal symptoms, further evaluation with synovial fluid analysis or joint ultrasonography was not performed. Lastly, as most musculoskeletal symptoms resolved during admission, there was no follow-up data after discharge, limiting an assessment of recurrence. However, strengths of the study should be acknowledged such as the originality of the clinical question leading to the study; and all cases of COVID-19 were diagnosed with RT-PCR rather than using a clinical diagnosis. A younger and relatively healthy cohort is less likely to have comorbidities such as osteoarthritis or gout, which can confound the observation of acute arthralgia in COVID-19 hospitalised patients.

Conclusion

The musculoskeletal manifestations of COVID-19 were characterised for the first time in this study. Reassuringly, it showed that the presence of musculoskeletal symptoms was not associated with developing a viral pneumonia in COVID-19. COVID-19-associated viral arthralgia in this cohort was a novel clinical entity that did not appear to be typical of a viral prodrome or of a reactive arthropathy, and had distinct characteristics from the other musculoskeletal presentations of COVID-19. Given the public health risk posed by COVID-19, clinician awareness is important, as acute respiratory symptoms may be absent at the time of presentation. Further studies are required to elucidate the underlying mechanism (s) of COVID-19-associated arthralgia and to ascertain its prognostic implications.

Ethical approval

This study was approved by the Institution Ethics Board of Woodlands Health Campus (DSRB 2020/00765).

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Conflict of interest

The authors declare no conflict of interest.

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None.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2021.01.031.

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