Skeletal muscles and Covid-19: a systematic review of rhabdomyolysis and myositis in SARS-CoV-2 infection

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Abstract

Objective

Myalgia is a widely publicised feature of Covid-19, but severe muscle injury can occur. This systematic review summarises relevant evidence for skeletal muscle involvement in Covid-19.

Methods

A systematic search of OVID and Medline databases was conducted on 16/3/2021 and updated on 28/10/2021 to identify case reports or observational studies relating to skeletal muscle manifestations of Covid-19 (PROSPERO: CRD42020198637). Data from rhabdomyolysis case reports were combined and summary descriptive statistics calculated. Data relating to other manifestations were analysed for narrative review.

Results

1920 articles were identified. From these, 61 case reports/series met inclusion criteria, covering 86 rhabdomyolysis cases. Median age of rhabdomyolysis patients was 50 years, (range 6-89). 49% had either hypertension, diabetes mellitus or obesity. 77% were male. Symptoms included myalgia (74%), fever (69%), cough (59%), dyspnoea (68%). Median peak CK was 15,783U/L. 28% required intravenous haemofiltration and 36% underwent mechanical ventilation. 62% recovered to discharge and 30% died. Dyspnoea, elevated CRP and need for intravenous haemofiltration increased risk of fatal outcome. Additional articles relating to skeletal muscular pathologies include 6 possible concomitant diagnoses or relapses of idiopathic inflammatory myopathies and 10 reports of viral-induced muscle injuries without rhabdomyolysis. Localised myositis and rhabdomyolysis with SARS-CoV-2 vaccination have been reported.

Conclusion

Rhabdomyolysis is an infrequent but important complication of Covid-19. Increased mortality was associated with a high CRP, renal replacement therapy and dyspnoea. The idiopathic inflammatory myopathies (IIM) may have viral environmental triggers. However, to date the limited number of case reports do not confirm an association with Covid-19.

Key words

rhabdomyolysis, idiopathic inflammatory myopathies, myositis, muscle, Covid-19, SARS-CoV2

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Introduction

Since the emergence of Covid-19 caused by SARS-CoV-2 infection, there has been a rush to share information on the clinical manifestations of this novel disease to aid clinicians amidst a global pandemic. The classical features of Covid-19 were initially reported as fever, cough and dyspnoea, however it quickly became evident that the infection can manifest with a vast array of different complications. Myalgia is a frequently reported symptom occurring in between 19 and 33% of patients (1, 2). Additionally, severe muscle inflammation and injury has been reported, including rhabdomyolysis leading to multi-organ failure and death.

Rhabdomyolysis describes a rapid disruption to the integrity of skeletal muscle leading to sudden release of muscle cell components such as myoglobin, creatine kinase (CK), aldolase, lactate dehydrogenase (LDH) and electrolytes, into the extra-cellular space and circulation. In severe examples this can lead to acute renal failure, disseminated intra-vascular coagulation and life-threatening electrolyte imbalances (3). Presenting features are variable with the classical triad of myalgia, weakness and myoglobinuria seen in <10% of patients, and myalgia or weakness in <50% (4). Viral triggers of rhabdomyolysis have been identified, with influenza A and B most commonly implicated, but also described with Human Immunodeficiency Virus, Coxsackie virus, Epstein-Barr Virus, Cytomegalovirus, Herpes Simplex Virus, Varicella Zoster Virus and West Nile Virus (3).

SARS-CoV-2 enters cells via the interaction of the viral spike protein domain and the angiotensin converting enzyme 2 (ACE2) on host cells (5). ACE2 is expressed in numerous different tissues, including skeletal muscle (6). It is plausible that SARS-CoV-2 can directly infect skeletal muscle cells via ACE2 as well as activating resident immune cells leading to direct viral damage and indirect immune mediated damage (7). Additionally, the systemic change in the cytokine milieu in response to infection includes an elevation in interleukin-6 (IL-6) which can disrupt muscle metabolic homeostasis, accelerating cell damage (8). Hyperlactataemia develops due to surplus cell damage, and exacerbates further muscle cell damage. Hyperlactataemia and metabolic acidosis inhibit the oxygen-carrying capabilities of erythrocytes contributing to hypoxaemia. In hypoxaemic conditions, anaerobic glycolysis in the muscles leads to an increase in lactate dehydrogenase (LDH) leading to excessive lactate production from pyruvate, intensifying the hypoxic ischaemia (9). Subsequent ATP depletion and disruption of the ion channels can propagate a self-sustaining myolytic cascade leading to necrosis of the muscle fibres and the release of muscle contents to the blood stream: rhabdomyolysis (3).

It has also been suggested that Covid-19 may trigger a chronic auto-immune mediated muscle injury; provoking or exacerbating idiopathic inflammatory myopathies (IIMs). IIMs describe a myriad of related conditions, often broken down into subgroups, including dermatomyositis (DM), polymyositis, juvenile dermatomyositis (JDM), immune-mediated necrotising myopathy and inclusion body myositis. They occur in isolation or alongside other mixed connective-tissue diseases and variably manifest in combinations of muscle weakness, characteristic skin rashes, interstitial lung disease and myocarditis.

Neuromuscular sequelae are frequently reported in Covid-19. Differential diagnoses for weakness in hospitalised Covid-19 patients include critical illness myopathy and polyneuropathy, and Guillain-Barré Syndrome (10-12). Whilst resulting in muscular symptoms, these neurological conditions are beyond the scope of this review which aims to gather and summarise available evidence relating to skeletal muscular damage in Covid-19.

Methods

We performed a systematic literature search according to pre-defined search protocols registered with PROSPERO (ID: CRD42020198637) to identify articles related to skeletal muscle pathology with Covid-19 on 16/3/2021 and updated on 28/10/2021. PubMed and Web of Science search engines were used to search OVID and Med-

line databases for the following terms: ["COVID-19" OR "SARS-CoV-2" OR "Coronavirus disease 2019" OR "Novel coronavirus" OR "2019-nCOV"] AND ["Myalgia" OR "Myositis" OR "Rhabdomyolysis" OR "Muscle"]. Articles were selected for inclusion if they represented original work relating to patients with confirmed Covid-19 with skeletal muscle pathology including letters to editor, case reports, case series, observational studies and conference proceedings. Cardiac muscle and neurological involvement were excluded, as were articles not available in English. In addition to exclusions listed in PROSPERO, as myalgia incidence in Covid-19 has been well described previously, articles with reference to only myalgia incidence and no further musculoskeletal manifestations were excluded. Reference lists of included articles were manually searched for additional articles. There is no validated tool for analysing risk of bias in case reports, though it may be expected they are written according to the CARE case report guidelines (13). All reports were assessed on the following CARE domains and excluded if there were significant concerns: Clinical findings, Diagnostic assessment, Therapeutic interventions, Outcomes.

Search and article selection was performed by 2 independent reviewers. Data was extracted into a pre-populated Excel spreadsheet by 3 researchers with a further researcher repeating for accuracy. Data disparities were resolved by discussion and mutual agreement with other members of the team. Quality of case reports was analysed against the stated CARE domains, and those providing insufficient clinical or diagnostic information to justify their conclusions were excluded if unanimously agreed between all team members. Missing data were assumed to be negative. Pooled descriptive statistics using simple frequency and proportions for categorical data and mean or median for continuous variables were calculated for rhabdomyolysis features including age, gender, co-morbidity, biochemical parameters and outcomes including mechanical ventilation, haemodialysis and death. A comparison of baseline characteristics of survivors and non-survivors was carried out using Chi^2 testing for binary variables, and Wilcoxon-Mann-Whitney test for continuous variables using a significance threshold of $p<0.05$. For non-rhabdomyolysis articles, statistical analysis was not completed due to small numbers of reports and heterogeneity between the case examples, so a narrative review of these articles is presented instead.

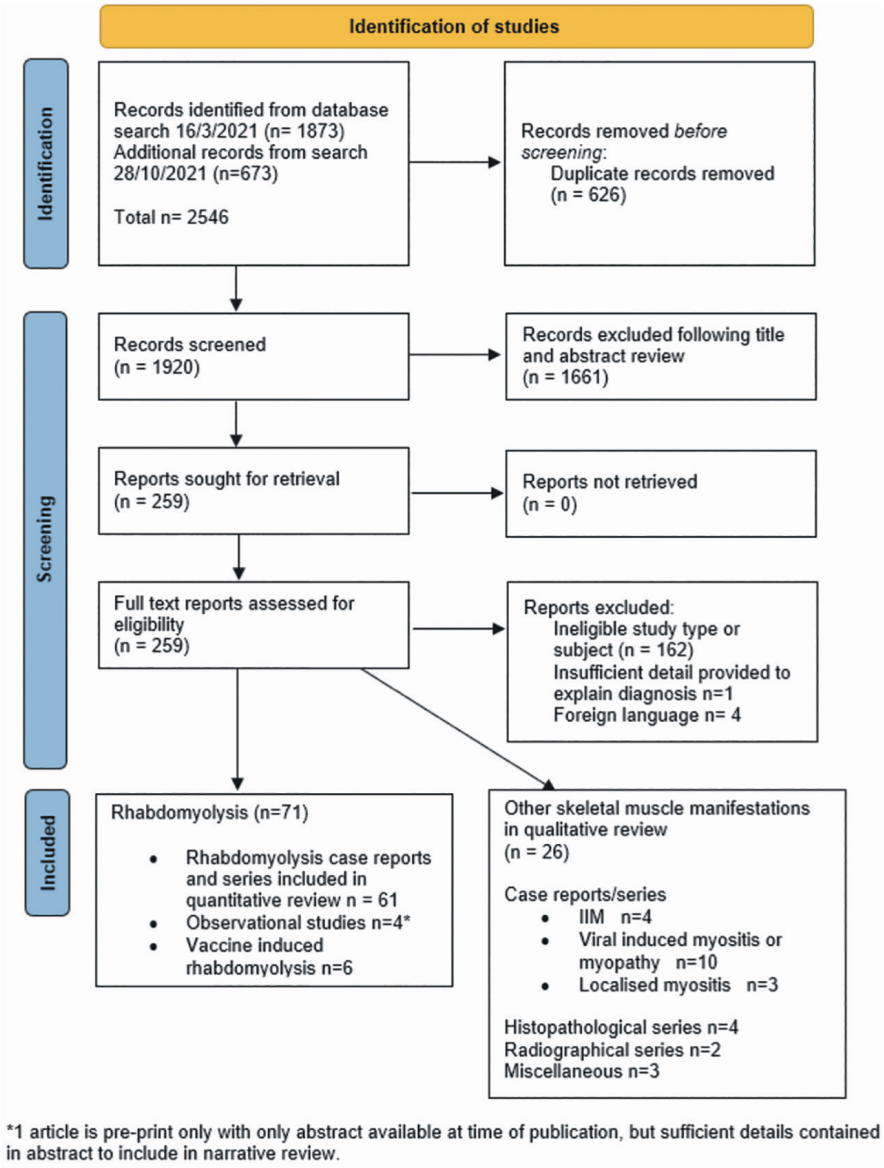

Fig. 1. PRISMA flow diagram detailing process for identification of studies for inclusion.

Results

Rhabdomyolysis

1873 articles were identified using the search protocol (Fig. 1), and an additional 673 on the updated search. This was narrowed to 61 case reports or series relating to rhabdomyolysis covering 86 unique cases (Supplementary Table S1) (14-74), 6 cases of vaccine-induced rhabdomyolysis (75-80), 4 observational studies (81-84), and 26 additional articles relating to alternative muscle pathology or study methodology suitable for qualitative review (85-110). One case report was excluded for not providing sufficient diagnostic information to suggest an aetiology to the patient's neuromuscular symptoms (111).

The average age of rhabdomyolysis patients was 50 years, though ranged from 6-89 years. There appears to be a bi-modal distribution (Fig. 2) with 17 patients under the age of 23. Four of

these (2 of which were fatal) had previous history of rhabdomyolysis, including one with a known genetic predisposition due to inborn error of fatty acid metabolism. No patients over the age of 23 reported a previous history of muscle disease.

77% cases were male and 49% had at least one other documented Covid-19 risk factor from hypertension, diabetes mellitus or obesity.

Common symptoms were myalgia (74%), fever (69%), cough (58%), dyspnoea (67%). Cardiac muscle involvement was also seen in 6 cases (7%), either myocarditis, myopericarditis, cardiomyopathy or acute coronary syndrome, with elevated troponins mentioned in another 7 reports. Median value for peak CK was 15783 IU/L and LDH, C-reactive protein, AST and ALT were also elevated at 751 U/L, 32 mg/dL, 186 U/L and 110 U/L respectively.

Quality and consistency of case reports was poor with elements of key data missing in all reports, making risk of bias universally high. Acute kidney injury was reported in 52% and haemoglobinuria or myoglobinuria in 36%, though this data was missing from up to half the papers. Drug history or indication that drug-induced causes had been considered were only provided in 41%. Six cases reported the prior use of statins.

Outcome was well reported with 36% requiring mechanical ventilation and 28% requiring renal replacement therapy. 62% recovered to discharge, 30% died and only 7% were still in hospital or outcome unspecified. Only two cases reported need for ongoing haemodialysis after discharge.

Pooled analysis of survivors *versus* non-survivors showed fatal cases had a significantly higher requirement for renal replacement therapy, higher baseline CRP and were more likely to complain of dyspnoea. A trend was observed that myalgia may reduce risk of mortality, but at p=0.051 it did not reach the threshold of statistical significance (Table I).

The only retrospective cohort study of ICU patients with rhabdomyolysis found that male sex, morbid obesity and prone positioning increased the likelihood of developing rhabdomyolysis (84).

Few observational studies describe incidence of rhabdomyolysis in Covid-19 with widely varying estimates. Three studies were identified with incidences of 16.9%, 2.2% and 0.2% (81-83). Only the larger estimate by Haroun *et al*. explicitly stated their definition of rhabdomyolysis: the sole requirement being CK >5 times upper limit of normal (82). Mokhtari *et al*. estimate rhabdomyolysis incidence within ICU patients at 48.5%. Again, the only diagnostic criterium was a CK>1000 (84).

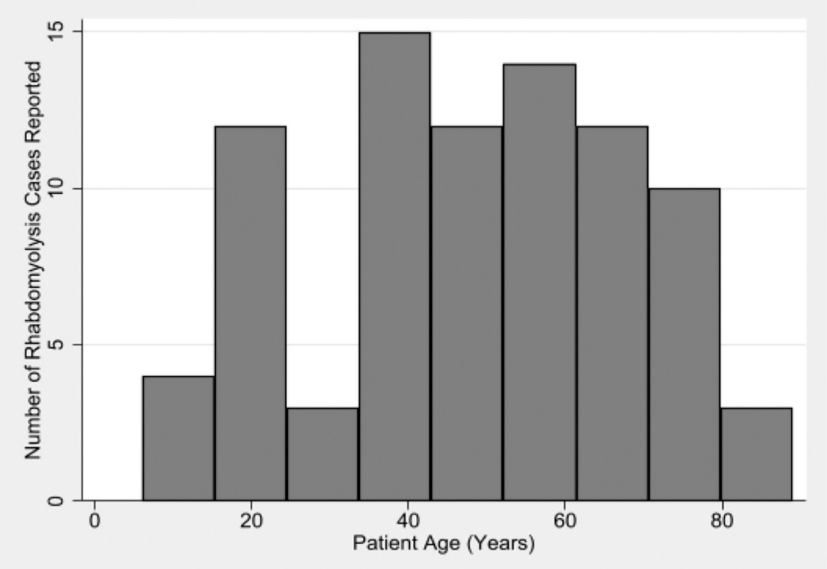

Fig. 2. Histogram demonstrating bimodal age distribution of rhabdomyolysis patients.

Table I. Differences in baseline characteristics between survivors and non-survivors in reports of Covid-19-associated rhabdomyloysis. Significance testing by Chi^2 or Wilcoxon-Mann-Whitney test. Statistically significant variables defined as p<0.05 displayed in bold typeface.

	Died	Survived	*p*-value
Number of patients, n	26	54	
Age	51.5	46.8	0.181
Male	81%	75%	0.627
Obesity, HTN or DM	45%	50%	0.867
Myalgia	50%	74%	0.051
Fever	65%	59%	0.598
Dyspnoea	**73%**	**48%**	**0.035**
Cough	58%	48%	0.424
AKI	58%	52%	0.624
Myoglobinuria	23%	41%	0.121
Peak CK (U/L)	13364	16078	0.572
Baseline LDH (U/L)	717	751	0.875
Baseline CRP (mg/dL)	**154**	**22**	**0.007**
Baseline AST (U/L)	128	475	0.078
Baseline ALT (U/L)	65	132	0.074
Mechanical ventilation	46%	33%	0.267
Renal replacement therapy	**46%**	**22%**	**0.029**

Covid vaccination

Covid-19 vaccination appears to have triggered localised myositis in one case, and full rhabdomyolysis in 6 other cases (Supplementary Table S2) (75-80, 94). This phenomena has been seen with 3 different vaccines, with both viral vector and mRNA vaccines implicated. Whilst several of the vaccine-associated cases were mild, 2/6 patients died, including one patient who developed associated myocarditis.

Viral myositis

Several articles report cases of virally induced myositis or myopathy (89-95, 107-109). Some describe various

degrees of skeletal muscle injury but without the associated rapid muscle cell breakdown and enzyme release of rhabdomyolysis (89, 90, 108). Others do describe substantial CK rise without the authors ever using the terminology rhabdomyolysis (91, 92, 95). All these cases likely fall in the same spectrum of muscle disorders as rhabdomyolysis. Localised myositis of the orbits resulting in swelling, discomfort and limitation of eye movements resolving with oral corticosteroid treatment has been reported (101, 102).

CK elevation can occur in Covid-19 even in the absence of fulminant rhabdomyolysis and appears be a marker of poor prognosis (110, 112). A meta-analysis of observational studies found 17% hospitalised patients had elevated CK, conferring a 49% probability of severe Covid-19 or death compared to 24% in those with normal CK (112).

Post-covid syndrome is an increasingly recognised phenomenon. One cohort reported long-term fatigue and muscle weakness in 63% of patients 6-months post-hospitalisation (113). Pathogenesis remains unclear, but myopathic EMGs have been seen in 55% of patients complaining of persistent neuromuscular symptoms post Covid-19 infection.(106)

Idiopathic inflammatory myopathy

Four articles report new diagnoses of idiopathic inflammatory myopathies (IIMs) coinciding with Covid-19 (85-88) and two groups report anecdotal increase in new onset IIMs during the pandemic (85, 100). Gokhale *et al*. present several cases but only 2 tested positive by SARS-CoV-2 PCR, both of whom described skin rashes, truncal and proximal weakness and interstitial pneumonia. The first had homogenous anti-nuclear antibody and showed excellent response to IVIG treatment (85). Their second was a fatal case with Melanoma Differentiation-Associated protein 5 (MDA-5) and SAE-1 antibody positivity requiring repeated testing over 7 days before SARS-CoV-2 infection was confirmed. Another of their cases describes a flare of disease in a known dermatomyositis patient associated with negative SARS-CoV-2 PCR but positive IgG and IgM antibodies.

Rodero *et al*. found serological evidence of simultaneous asymptomatic Sars-CoV-2 infection in 2/10 cases of JDM diagnosis or relapse (20%) (88). Neither carried a myositis-specific antibody, though both convincingly met accepted JDM classification criteria. IFNα2 level was substantially elevated above the median in both cases supporting the suggestion of a type 1 interferonopathy being a critical driver of Covid-19 and IIM.

Of the two further articles purporting to describe new onset IIM, one tested positive for SAE-1 antibody. In this report, the patient's initial SARS-CoV-2 PCR test was negative and only became positive on repeat testing 3 weeks after initial presentation (87). CK was more modestly elevated at 700 U/L, substantially less than for the rhabdomyolysis patients. In the other report the patient presented with interstitial pneumonia due to Covid-19 but went on to develop Anti-Ku and Anti-Mi2b antibodies on repeat testing (86).

Of the four potential adult IIM cases, only one (Gokhale *et al*. Case 1) was reported in sufficient detail to complete either the 2017 EULAR/ACR classification guidelines for IIMs, or the traditional Bohan and Peter diagnostic criteria, to confirm probable dermatomyositis diagnosis (114).

Muscle biopsies

Muscle biopsy is not usually required in rhabdomyolysis. Several autopsy studies have looked at series of muscle specimens from patients known to have died from Covid-19 and found between 20-60% have inflammatory muscle changes (96-99). One study found necrotising myopathy in 9/35 and myositis (defined as perivascular and endomysial inflammatory cell infiltrate) in 7/35 consecutive autopsies (99). Another study found inflammatory muscle change in 26/43 specimens. No evidence of direct viral invasion was detected by immunohistochemistry or electron microscopy in any of these series, however some muscle specimens showed evidence of SARS-CoV-2 RNA using reverse transcription (98).

Muscle imaging

Magnetic resonance imaging (MRI) can be a useful modality for investigating muscle inflammation. Findings included bilateral muscle oedema (43, 60, 85, 87, 91). One case reported high attenuation foci felt to be calcifications secondary to rhabdomyolysis (43). Changes may also be seen in the muscles in those not known to have muscular involvement. A cohort of 9 patients undergoing spinal MRI imaging found 7/9 had bilateral paraspinal muscle oedema in the lumbar region. This was out of proportion to any subcutaneous oedema seen, thereby implying muscular pathology rather than dependent oedema (93).

Discussion

Rhabdomyolysis

Based upon the information in this systematic review, the estimated incidence of rhabdomyolysis is between 0.2-2.2% of hospitalised Covid-19, although asymptomatic muscle enzyme elevations are more frequent. CK elevation has been associated with an overall increase in mortality, regardless of the development of rhabdomyolysis (110, 112).

Baseline characteristics mirror those at highest risk from Covid-19, with high levels of obesity, diabetes or hypertension and a high proportion of males. Patients are generally younger than one might expect for hospitalised Covid-19 patients, and there is a group of adolescents and young adults with preceding rhabdomyolysis history suggesting underlying predisposing conditions. Mortality estimates for Covid-19 will vary according to time within the pandemic and geographical location. Previous meta-analysis of in-patient mortality in Covid-19 estimates mortality at 12% (95% CI 9-15%) (115). Whereas our pooled analysis of rhabdomyolysis Covid-19 patients found a higher mortality of 30%.

Many drugs can trigger rhabdomyolysis, with statin medications and certain antibiotics particularly implicated. Many of the reported cases developed rhabdomyolysis during their hospitalisation rather than at admission. In some of these cases antibiotics including

azithromycin, and piperacillin-tazobactam have been administered, which are known culprits in drug-induced rhabdomyolysis (116). Given the high proportion of patients with obesity and hypertension, it is surprising that pre-morbid statin use has only been described in five cases. The majority of reports showed little evidence that drugs as causative or contributory agents had been considered.

There is a lack of consensus in the nomenclature of myopathic events. Myalgia, viral induced muscle injury, myopathy, myositis, rhabdomyolysis are all commonly used terms. Confusion over terminology could lead to muscle injury events being under-reported and under-diagnosed. In 2002 the American College of Cardiology (ACC), American Heart Association (AHA), and National Heart, Lung, and Blood Institute (NHLBI) defined rhabdomyolysis as the elevation of CK (typically >10 times the upper limit of normal), creatinine elevation, and usually brown urine or myoglobinuria; but this is not widely used in clinical practice as evidenced by the none of the cohort studies and a majority of case reports not meeting or including all these diagnostic details (117).

Idiopathic inflammatory myopathies

Our systematic review found six reports implicating proven SARS-CoV-2 infection in the direct development of IIM. Only half were reported in sufficient detail to satisfy commonly used diagnostic and classification criteria, casting doubt over the diagnostic accuracy of the remaining three cases. Sacchi *et al*. described the case of Covid-19 pneumonia with weakness that later became Anti-Ku and Anti-Mi2b positive, with symptoms and antibodies persisting 2 months later suggesting the development of a chronic autoimmune condition (86). Conversely, the case from Zhang *et al*. of SAE-1 associated myositis developed muscle symptoms first with a three-week delay before Covid-19 was confirmed casting doubt on a temporal causal association. Given the endemicity of Covid-19, this infection could conceivably be coincidental or even hospital-acquired (87). Likewise one of the cases from Gokhale *et al*. only tested positive on later PCR swabs, so causative relationship remains unclear. This case had anti-MDA-5 antibodies which produce a variant of IIM that can present similarly to Covid-19 pneumonia and has a high mortality rate, so further details would be useful to differentiate the two potential aetiologies to this patient's fatal pneumonia (85).

In a midst of a pandemic, it is tempting to draw associations between rare unrelated events and Covid-19. Nevertheless, there is hypothetical plausibility that IIM development and Covid-19 could be linked.

The aetiology of IIMs is largely unknown. Some have hypothesised that viruses can trigger these rare autoimmune conditions through breaking self-tolerance in genetically susceptible individuals. Evidence for a possible infectious aetiology includes apparent seasonal variability in diagnoses, with anti-Jo1 anti-synthetase diagnoses clustering in Spring, and anti-SRP positive necrotising myopathy in the Autumn (118). Other studies have reported an increase in respiratory or gastrointestinal infections preceding juvenile dermatomyositis (JDM) and adult-onset IIM (119, 120). Coxsackie B, parvovirus, enterovirus, Human T-cell lymphotropic Virus 1 and HIV have all been proposed as triggers (121).

There are parallels in the pathogenesis of IIMs and Covid-19 (105, 122-127). Specifically anti-MDA-5 DM frequently presents with fevers, rash, arthralgias, myalgias, acute interstitial pneumonia and a thrombotic vasculopathy, all also notable features of Covid-19. Kondo *et al*. observed similar hyperinflammatory states between the two conditions, with pro-inflammatory cytokines, hyperferritinaemia and macrophage activation syndrome commonly seen in both (125). Activation of macrophages/monocytes and cell pyroptosis contributes to the development of cytokine storm which accelerates lung inflammation and progression to acute respiratory distress syndrome (ARDS) in Covid-19 and anti-MDA-5 DM (126, 127). The striking similarities may indicate a shared pathogenic link; potentially involving the MDA-5 receptor, a pattern recognition receptor capable of detecting viruses and triggering a type 1 interferon response (128). In health, the MDA-5 receptor has a role in innate immunity against viruses, including SARS-CoV-2 (129).

Myositis specific autoantibodies are a frequent feature of IIM, though whether they are biomarkers or have a direct pathogenic role remains debatable (130). Anti-TIF-1-Gamma antibodies seen in a subset of dermatomyositis patients have immune epitopes of high sequence identity to those of SARS-CoV-2, leading the authors to speculate that coronaviridae exposure may contribute to the development of IIMs (131).

There have been several reports of SARS-CoV-2 leading to the development of ither autoimmune conditions, most famously the multi-systemic inflammatory syndrome in children (MIS-C) variant of Kawasaki disease, but also Guillain-Barré syndrome, idiopathic thrombocytopenic purpura and autoimmune haemolytic anaemia, and antiphospholipid syndrome (132, 133). However, whilst pathologically feasble, further data are needed to confirm a true association between IIM and Covid-19.

Limitations

The conclusions from this systematic review are limited by substantial probability of publication bias. Particularly severe or "unusual" cases are more likely to be written up for publication. Seemingly unfavourable prognosis of the patients in our analysis should be interpreted in context of this and of improving mortality trends through the pandemic as understanding of the disease increases.

Case reports often lack sufficient detail to draw firm conclusions that a purported diagnosis of rhabdomyolysis or IIM is correct. Of particular note, it was rarely clear alternative causes of rhabdomyolysis had been considered.

Descriptive terminology for muscle injuries is not well defined, with clear discordance between papers. The lack of consistent definition of rhabdomyolysis makes estimation of true incidence and generalisation of results difficult.

Observational studies are now required to describe incidence and outcomes of rhabdomyolysis and the optimal management.

Care should be taken not to over-interpret the presence of a temporal association of IIM diagnosis and Covid-19. The vast volume of novel Covid-19 cases globally during the last 18 months increases the likelihood of rare diagnoses being mistakenly causally associated.

Conclusions

Rhabdomyolysis and milder degrees of skeletal muscle injury are features of SARS-CoV-2 infection. In the general hospital population CK has previously been correlated with severe Covid-19 and mortality and should be checked routinely as a marker of the hyperinflammatory state. Rhabdomyolysis is a potentially life threating complication. Amongst those with rhabdomyolysis, CK was not associated with poor prognosis, but high CRP, requirement for renal replacement therapy and the presence of dyspnoea were. Myalgia was predictive of a good outcome. In rhabdomyolysis cardiac involvement must be considered, as co-existing myocarditis, pericarditis and acute coronary syndrome have all been reported.

Rhabdomyolysis may be triggered by direct viral damage or through the effects of inflammation, though toxic drug-induced damage should always be considered. Covid-19 vaccination can also trigger rhabdomyolysis. Children and young adults can be affected, and clinicians should be alert for underlying genetic causes.

This study has not confirmed a causal link between Covid-19 and IIMs, however there have been reports of temporal association, and potential pathogenic similarities between the conditions exist. As research in the field continues to develop, severe Covid-19 and anti-MDA-5 DM may prove useful clinical models of each other. Screening for myositis specific or associated antibodies, muscle MRI and muscle biopsies are not routinely warranted in cases of elevated CK in Covid-19, though they should always be considered where there is specific clinical concern of an underlying IIM or alternative pathology.

Quality of evidence is poor, and there are substantial inconsistencies in classification and nomenclature of skeletal muscle injuries. Further high-quality observational studies are required to define incidence and long-term prognosis in these patients and improved international consensus on the description and grading of muscle injuries would be valuable to assist this.

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