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REVIEW

Comorbidities in rheumatic diseases need special consideration during the COVID-19 pandemic

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Abstract

Comorbidities in rheumatic and musculoskeletal diseases (RMDs) not only increase morbidity and mortality but also confound disease activity, limit drug usage and increase chances of severe infections or drug-associated adverse effects. Most RMDs lead to accelerated atherosclerosis and variable manifestations of the metabolic syndrome. Literature on COVID-19 in patients with RMDs, and the effects of various comorbidities on COVID-19 was reviewed. The initial data of COVID-19 infections in RMDs have not shown an increased risk for severe disease or the use of different immunosuppression. However, there are some emerging data that patients with RMDs and comorbidities may fare worse. Various meta-analyses have reiterated that pre-existing hypertension, cardiovascular disease, stroke, diabetes, chronic kidney disease, heart failure, lung disease or obesity predispose to increased COVID-19 mortality. All these comorbidities are commonly encountered in the various RMDs. Presence of comorbidities in RMDs pose a greater risk than the RMDs themselves. A risk score based on comorbidities in RMDs should be developed to predict severe COVID-19 and death. Additionally, there should be active management of such comorbidities to mitigate these risks. The pandemic must draw our attention towards, and not away from, comorbidities.

Keywords Musculoskeletal disease · Inflammatory arthritis · Connective tissue disorders · Comorbidities · COVID-19 · Metabolic syndrome

Introduction

Comorbidities are additional disease states or organ involvement that exist parallel to an index disease, and can delay diagnosis, confound the assessment of disease status, jeopardise treat-to-target strategies and reduce the quality of life or increase mortality [1]. Rheumatic and musculoskeletal diseases (RMDs) are chronic conditions that accrue damage as well as comorbidities over the years. An initiative from the European League Against Rheumatism (EULAR) stresses six significant comorbidities that need to be addressed in RMDs: ischaemic cardiovascular diseases, depression, infections, gastrointestinal diseases, osteoporosis and malignancies [2].

The most common comorbidity is likely cardiovascular. The risk of a myocardial event is at least 50% higher in patients with rheumatoid arthritis, gout and psoriatic arthritis than for the general population [3]. The risk is also higher for patients with osteoarthritis, and possibly for those with ankylosing spondylitis [3]. In chronic painful conditions like arthritis, there is catastrophising and thus, concomitant depression arising out of such inadept defence mechanisms [4]. Also, the chronic inflammation predisposes to neuroendocrine suppression, fatigue, sarcopenia, osteopenia and possibly a lean variant of the metabolic syndrome ("cachectic obesity") [5]. A meta-analysis has shown that

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patients with rheumatoid arthritis (RA) are at higher risk for lymphoma and lung malignancies [6]. All these comorbidities including cardiovascular disease, diabetes, osteoporosis, neoplasms, depression, and infections are often sub-optimally diagnosed and managed [2].

Comorbidities in RMDs have gained an extreme significance as they may be associated with increased risks of hospitalisation and death in the wake of the coronavirus-19 (COVID-19) pandemic. Preliminary data from patients with RMDs in Spain have shown that the presence of comorbidities as well as disease activity were associated with severe COVID-19 and death [7]. The initial cohort of patients with RMDs who had developed COVID-19 in Wuhan, China, included 17 patients, of which at least nine had comorbidities and one of these patients expired. Follow-up interviews of the 16 discharged patients revealed that 10 of them had discontinued or changed their rheumatology drugs [8]. Similarly, the report of the first 600 patients in the COVID-19 Global Rheumatology Alliance (C19-GRA) physician-reported registry also reiterated that age above 65 years and presence of comorbidities were more likely to be hospitalised [9].

Therefore, it is important to appraise the various comorbidities in RMD in the context of risk for COVID-19, and also, to anticipate how the pandemic influences the management and the prevention of comorbidities in RMDs. Closely entwined is the question of whether exposure to the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) in patients with RMDs would increase the risk of future comorbidities (Fig. 1).

Search strategies

Searches were carried out on MEDLINE/PubMed and Scopus in the first week of Oct 2020 for the literature on COVID-19 in RMD patients as per standard recommendations [10]. The common keywords used for the first search were "rheumatic disease", "inflammatory arthritis", "rheumatic and musculoskeletal diseases" in various combinations with "COVID-19" or "SARS-CoV-2". The second search included "COVID-19"or "SARS-CoV-2" with different combinations with "comorbidities", "metabolic syndrome", "diabetes", "hypertension", "lung disease", "cardiovascular disease", "stroke" and "myocardial infarction". The third search used "rheumatic disease", "inflammatory arthritis", or "rheumatic and musculoskeletal diseases" with the different comorbidities keywords included in the second search. The searches were updated in the third week of November to include any articles published since the initial searches.

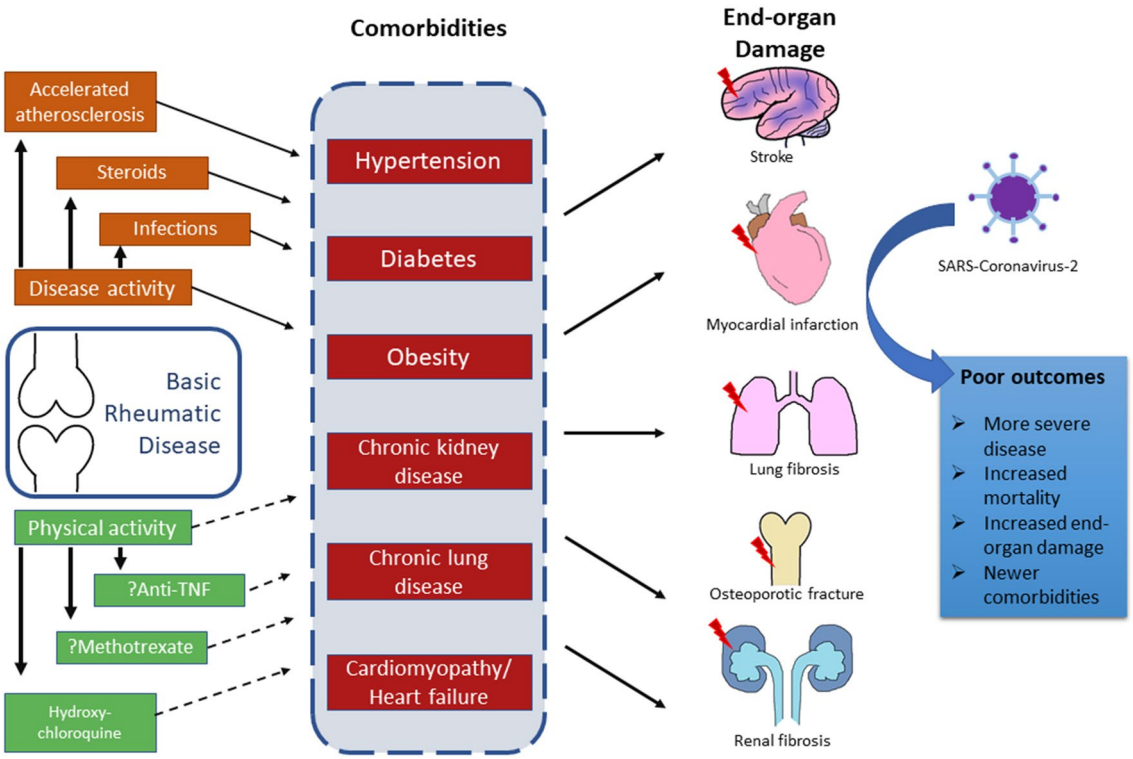

Fig. 1 Comorbidities and COVID-19

COVID-19 in RMD patients

In the initial data from China, there were 21 patients with RMDs and length of hospital stay was similar to those without RMDs [11]. A retrospective study from Spain has shown a higher prevalence of hospital diagnosed COVID-19 was more in patients on biologicals but in those on conventional DMARDs [12]. The results are summarised in Table 1. Telephonic or internet-based surveys estimating the incidence of infection without mentioning comorbidities have not been included in this table. Studies having higher co-morbidities seem to have more severe cases, often attributing it to the presence of RMDs. However, in studies with lower co-morbidities, there appears to be no difference of COVID-19 severity in RMDs and general populations. For patients with RMDs, prior knowledge about avoiding infections may play a role in reducing SARS-CoV-2 infection [13].

Comorbidities and death in COVID-19

In one of the first retrospective cohorts published from Wuhan, China, almost 50% of patients hospitalised with COVID-19 had comorbidities [36]. In the first 200 patients admitted in New York, the three most common comorbidities were hypertension (76%), hyperlipidemia (46.2%), and diabetes (39.5%) [37]. In an analysis of 3626 patients regarding the effects of race on COVID-19 outcomes, a higher score on the Charlson Comorbidity Index was associated with increased rates of hospitalisation [38]. Thus, comorbidities are common in patients with COVID-19. Table 2 summarises various meta-analyses looking at the associations of multiple comorbidities with mortality or severe disease in COVID-19.

One meta-analysis looking at patients with autoimmune diseases developing COVID-19 found no association with severe disease (3 studies, 1276 patients, OR = 1.21, 95% CI: 0.58–2.50, $p = 0.79$) or with mortality (3 studies, 835 patients, OR = 1.31, 95% CI: 0.33–5.20, $p = 0.95$) [56]. However, it should be kept in mind that the RMDs may be only a part of all autoimmune diseases, and the numbers are too small to analysis those with comorbidities.

Comorbidities in RMD that may predispose to severe COVID-19 and death

The different co-morbidities in various RMDs have different prevalence. Patients with difficult to control diseases often have higher comorbidities [57]. The most common comorbidities in each are enumerated in Table 3. Paediatrics patients often have limited comorbidities, and a systematic review has identified only one single child with RMD who had acquired COVID-19 [58].

Metabolic syndrome

Rheumatoid arthritis is associated with most facets of the metabolic syndrome. A meta-analysis has shown that the presence of RA is a risk factor for developing diabetes [97]. The system inflammation in RA, along with the use of glucocorticoids, has been implicated in the development of insulin resistance in RA [98]. This can be closely associated with obesity. At least a quarter of RA patients are overweight (BMI > 25) [62]. Besides being a direct risk factor, it also contributes indirectly by increasing disease activity and making remission more difficult to achieve [99]. Hypertension can be seen in around 50% of RA and is possibly more in patients with resistant disease [57]. Also, underdiagnosis and undertreatment of hypertension and dyslipidaemia in RA are reported [63]. The relationship of psoriatic arthritis with metabolic syndrome is stronger with common mechanistic pathways leading to both [100]. The cardiovascular risks of various rheumatic diseases have been explored in depth in various reviews [101, 102].

Accelerated atherothrombosis at premature age

The metabolic syndrome, as well as the pro-inflammatory state, leads to accelerated thrombosis. COVID-19 is intrinsically a pro-thrombotic state [103]. Thus, the risk of thrombosis may be multiplied in the setting of COVID-19.

Interstitial lung diseases

Amongst lung diseases, interstitial diseases (ILD) have the highest association with rheumatic disease. In RA, it is reported to have a prevalence from 1–60% depending on the methodology used [67]. Many of these patients may not be symptomatic, and only a proportion will have progressive lung disease. However, it is not known whether this will predispose to severe lung COVID-19. ILD are often a major concern in patients with systemic sclerosis (SSc) and with idiopathic inflammatory myopathies (IIM). ILD is the most frequent cause of death in SSc [104]. Registry data show around 40–50% of SSc patients are documented to have ILD [105]. A similar proportion of patients with mixed connective tissue disorder have ILD that is slowly progressive and increases the mortality rate [106]. Also, in the spectrum of IIM, the presence of ILD has been associated with 50% excess mortality [107]. ILD in Sjogren is reported from 8–35% with a 5-year survival of 84% [93, 108, 109].

Table 1 Summary of the available literature on COVID-19 in RMDs

Place	Cohort	Number of patients with RMDs	Comorbidities	Outcomes	References
Global	COVID-19 global rheumatology alliance physician-reported registry	600	33% had hypertension, 21% lung disease, 12% diabetes, 11% CAF and 7% chronic renal insufficiency	Patients admitted had a higher prevalence of these 5 co-morbidities	[9]
Wuhan, China	2326 patients with COVID-19 admitted to Tongji Hospital	21	Not mentioned	Mortality same in RMD and non-RMD patients	[11]
Massachusetts, USA	2154 patients with a positive test result for SARS-CoV-2	52	65% had hypertension, 25% had diabetes, 23% had CAD,	Those with rheumatic disease required intensive care admission and mechanical ventilation more often	[14]
Spain	Patients with COVID-19 in BIOBADASER	31	Hypertension (36.6%), diabetes (9.8%) and high body mass index mean (SD):27.7 (5.6) kg/m^2	Mortality in patients with RMDs treated with b/tsDMARD do not differ from the general population	[15]
Madrid, Spain	Patients with AIRD and COVID-19	123	32.5% had hypertension, 7.3% diabetes, 12.2% heart disease and 4.9% kidney disease	Having a systemic autoimmune condition increased the risk of hospital admission, whereas disease-modifying antirheumatic drugs were not associated with hospital admission	[16]
Madrid, Spain	PCR + COVID-19 rheumatic patients with matched controls	456	43% had hypertension, 17% had diabetes, 16.6% had obesity, 18.4% had CAD while 21% had lung disease	Previous comorbidity (obesity, diabetes, hypertension, cardiovascular or lung disease) increased the risk in the rheumatic cohort by bivariate analysis	[17]
Madrid, Spain	RMDs and COVID-19	122	39.3% had hypertension, 14% had diabetes, 23.6% had obesity, 17.2% had CAD while 16.4% had lung disease	Mortality was limited	[18]
Italy	RMDs and COVID-19, the CONTROL-19 surveillance database	232	45% had hypertension, 12% had diabetes, 14% had obesity, 22% had CAD while 31% had lung disease	Immunomodulatory treatments were not significantly associated with an increased risk of intensive care unit admission/mechanical ventilation/death	[19]
Leon, Spain	3711 patients with COVID-19	38	60.5% had hypertension, 39.5% had diabetes, 21% had lung disease	Comorbidities, rheumatic disease activity and laboratorial abnormalities were significantly associated with mortality	[7]
Hubei, China	568 patients admitted in The Central Hospital of Xiaogan	5	2 had hypertension; 2 had lung disease	More likely to progress into severe or critical COVID-19	[20]
Udine, Italy	1051 patients on biologic agents or small molecules	4	1 had hypertension, 2 had lung disease, 1 had heart disease	Risk for patients under biologic agents or small molecules does not appear different	[21]
Germany	Nationwide online database	104	Data not mentioned	More comorbidities (> 2) were documented in hospitalised patients than in non-hospitalised	[22]
Case-based review	Patients on Secukinumab who developed COVID-19	5	3 had hypertension	Disease course was mild in most patients	[23]

Table 1 (continued)

Place	Cohort	Number of patients with RMDs	Comorbidities	Outcomes	References
Madrid, Spain	RMD with COVID-19	62	45% had hypertension, 20% had diabetes, 33% had obesity, 52% had CAD while 23% had lung disease	Male gender, cardiovascular disease, hypertension, and diabetes were associated with a more severe infection requiring hospital admission	[24]
Madrid, Spain	RMD patients in rituximab with suspect or proven COVID-19	13	8 had hypertension, 1 had diabetes, 3 had CAD, 7 had pre-existing lung disease	There was high rates of hospitalisation and mortality, but comorbidities can act as confounders	[25]
Hong Kong	COVID-19 positive amongst 39,835 patients with RMD	5	1 had both diabetes and hypertension	All improved without complications	[26]
New York, USA	RMD with COVID-19	4	2 had hypertension, 1 had ILD with chronic renal insufficiency	1 patient remained on ventilator	[27]
Barcelona, Spain	COVID-19 in RMD on targeted biologic and synthetic DMARD	11	1 had hypertension, 2 heart disease, 1 diabetes and renal insufficiency	Patients did not have more severe disease	[28]
Brescia, Italy	COVID-19 positive amongst 1525 patients with RMD and matched controls	65	51% had hypertension, 14% had diabetes, 12% had CAD, 17% had obesity and 11% had lung disease	Poor outcome from COVID-19 associated with older age and comorbidities rather than the type of rheumatic disease or immunosuppression	[29]
Hubei province, China	Telephonic survey on 6228 patients with RMDs	27	Data not provided	Patients with RMDs might be more susceptible to COVID-19 as compared to their family members	[30]
Brussels, Belgium	RMD with COVID-19	23	30% had hypertension, 17% had diabetes, 9% had heart disease, 9% had obesity,4% had kidney disease and 17% had lung disease	All patients with severe COVID-19 had co-morbidities	[31]
Ouagadougou, Burkina Faso	RMD with COVID-19	5	1 had hypertension and asthma while another had heart disease and a third had chronic kidney disease	Only patient with CKD had severe COVID-19	[32]
Southampton, UK	1004 RMD patients on bDMARDs or tsDMARDs	2	1 had hypertension and CAD	Only 7 suspect patients were tested	[33]
Dublin, Ireland	Online survey with 1381 respondents having RMDs	6	Not mentioned	Similar risk as non-RMD patients	[34]
France	Online survey with 655 respondents having RMDs	12	Not mentioned	Out of the 12, 5 were negative on RT-PCR but were diagnosed with CT chest	[35]

Table 2 Meta-analyses on effects of comorbidities on COVID-19

Condition	Included	Results of meta-analysis	References
Cancer	10 studies	RR for death = 1.47 (95% CI: 1.01–2.14)	[39]
Cardiovascular disease	13 studies 3027 patients	OR for critical/mortal patients = 5.19, 95% CI (3.25, 8.29)	[40]
	16 studies with 4448 patients	RR for death = 2.25 (95% CI: 1.53, 3.29)	[41]
	14 studies	RR for death = 2.25 95% CI (1.60–3.17)	[39]
	Seven studies with 1576 patients	OR for severe disease = 3.42 (95% CI: 1.88–6.22)	[42]
Cerebrovascular disease	Six studies with 1527 patients	RR for severe disease = 3.30, 95% CI (2.03, 5.36)	[43]
	16 studies with 4448 patients	RR for death = 2.38 (95% CI: 1.92, 2.96)	[41]
Chronic kidney disease	Nine studies	RR for death = 3.25 (95% CI: 1.13–9.28)	[39]
Congestive heart failure	Three studies	RR for death = 2.03 (95% CI: 1.28–3.21)	[39]
COPD	15 studies with 2473 patients	RR for sever disease = 1.88 (95% CI 1.4–2.4)	[44]
	Eight studies	RR for death = 1.33 (95% CI: 0.77–2.31)	[39]
Diabetes	Seven studies with 1576 patients	OR for severe disease = 2·07 (95% CI 0·88–4·82)[a]	[42]
	13 studies 3027 patients	OR for critical/mortal patients = 3.68 95% CI (2.68, 5.03)	[40]
	30 studies with 6452 patients	RR for death = 2.12 95% CI (1.44, 3.11)	[45]
	13 studies with 926 patients	OR for death = 1.75 95% CI (1.31–2.36)	[46]
	Four studies with 471 patients	OR for death = 3.21 95% CI (1.82–5.64)	[47]
	Six studies with 1687 patients	RR for severe disease = 2.26 (95% CI: 1.47–3.49)	[48]
	65 studies with 15,794 patients	RR for death = 2.78 (95% CI: 1.39–5.58)	[49]
	Six studies with 1527 patients	RR for severe disease = 2.21, 95% CI (0.88, 5.57)[a]	[43]
	33 studies with 16,003 patients	OR for death = 1.90 (95% CI: 1.37–2.64)	[50]
	16 studies	RR for death = 1.48 (95% CI: 1.02–2.15)	[39]
Hypertension	19 studies with 15,302 cases	Adjusted OR for death = 1.44, 95% CI (1.24–1.66); $I^2 = 41.4\%$	[51]
	Seven studies with 1576 patients	OR for severe disease = 2.36 (95% CI: 1.46–3.83)	[42]
	13 studies 3027 patients	OR for critical/mortal patients = 2.72, 95% CI (1.60,4.64)	[40]
	12 studies with 2389 patients	OR for death = 3.48 (95% CI: 1.72–7.08)	[52]
	Three studies with 419 patients	OR for death = 3.36 (95% CI: 1.96–5.7)	[53]
	65 studies with 15,794 patients	RR for death = 2.39 (95% CI 1.54–3.73)	[49]
	six studies with 1527 patients	RR for severe disease = 2.03 95% CI (1.54, 2.68)	[43]
	30 studies with 6560 patients	RR for death = 2.21 (95% CI: 1.74, 2.81)	[54]
	13 studies	RR for death = 1.82 (95% CI: 1.43–2.32)	[39]
Obesity	Six studies with 26,507 patients	OR for death = 3.68 95% CI (1.54–8.83)	[55]
Respiratory system	Seven studies with 1576 patients	OR for severe disease = 2.46 (95% CI: 1.76–3.44)	[42]
	13 studies 3027 patients	OR for critical/mortal patients = 5.15, 95% CI (2.51, 10.57)	[40]

Chronic kidney disease

Patients with lupus nephritis may develop chronic kidney damage including interstitial fibrosis and glomerulosclerosis. Similarly, patients with Sjogren and long-standing RA may also develop features of chronic kidney disease (CKD). A meta-analysis of cohort studies has shown that patients with RA have a higher incidence of developing CKD [110]. Though previously, it was attributable to the high use of non-steroidal anti-inflammatory drugs, and uncontrolled inflammation (leading to amyloidosis), currently, it is more likely to be associated with accelerated atherosclerosis [111]. Though the mortality in lupus has come down drastically in the last 2 to 3 decades, renal impairment is still seen in up to 40% of patients [85]. Scleroderma renal crisis, though uncommon, is the leading cause of renal transplantation in SSc patients, and 5 years mortality after transplant is 82.5% [112]. It is well known that COVID-19 can directly precipitate acute kidney injury (AKI) and presence of CKD is a poor prognostic marker.

Effects of depression

The association between inflammatory rheumatic diseases and depression is well established. A meta-analysis has shown that depression is prevalent in at least one-third of patients with RA [113].

Immunomodulatory therapy seems to improve mental parameters independent of improvement in physical disease activity [114]. Conversely, it is expected that depression

Table 3 Prevalence of various comorbidities in RMDs

Disease	Co-morbidity that may predispose to severe COVID-19	Estimated prevalence (%)	References
Rheumatoid arthritis	Metabolic syndrome	14–38	[59, 60]
	Hypertension	23–66	[61–63]
	Obesity	11.4–39	[62, 64]
	Diabetes	14–20	[57, 61, 62, 65]
	ILD	1–58	[66, 67]
	Cardiovascular disease	5.6–21.3	[64, 68]
Psoriatic arthritis	Metabolic syndrome	33–40.6	[69–71]
	Hypertension	24–55	[72, 73]
	Obesity	6–27.6	[74, 75]
	Diabetes	7.3–13.8	[76, 77]
	Coronary artery disease	10–60	[78, 79]
Other spondyloarthritis	Cardiovascular disease	16.5	[80]
	Hypertension	10–22.4	[80–82]
	Diabetes	5.5–10.1	[80, 81]
	Aortic insufficiency	2.9–18	[80, 83]
Systemic lupus erythematosus	Chronic renal insufficiency	6.7–40	[84, 85]
	Hypertension	8.6–77	[86]
	Pulmonary hypertension	2.3	[87]
	Coronary artery disease	52.8	[88]
Systemic sclerosis	ILD	40–80	[89, 90]
	Pulmonary hypertension	20–31.2	[89, 91]
Primary Sjogren syndrome	Chronic kidney disease	50	[92]
	ILD	3–11	[93]
ANCA associated vasculitis	Lung disease	14–85	[94]
	Chronic renal insufficiency	8	[95]
Takayasu arteritis	Resistant hypertension	8.2	[96]

would also alter immune parameters in an individual. It can alter the hypothalamic–pituitary–adrenal axis and sympathetic outflow [4]. Depression is associated with immune dysregulation, independent of RMDs [115]. This may predispose to infections and possibly even severe COVID-19. In mice models, it has been shown that repeated social defeat leads to immune suppression [116]. Though there may be a risk of confounding by indication, a cohort of 59,301 people followed up for 14.8 years has shown that those with depression have a higher incidence of blood-stream infections [117].

Risk of infections

RMDs are independently associated with the risk of infections [118]. The various disease-modifying anti-rheumatoid drugs (DMARDs) are immunomodulatory agents. Especially the use of targeted synthetic and biological DMARDs possibly predispose to a higher rate of infections including opportunistic infections [119]. Though rituximab has been implicated to have a higher risk of infections as compared to other biologicals, a meta-analysis has shown no difference [120].

People with RMDs usually have poorer compliance with vaccination [121] though they are often at increased risks for various infections including pneumococcal, meningococcal, herpetic and other vaccine-preventable infections [122].

Risk stratification for severe COVID-19 and death in RMDs

Quantifying the risks for severe COVID-19 and mortality is required. A risk score to predict this will need to include the number of comorbidities providing a weightage score based on the severity and duration of each. The previous history of infections, hypogammaglobulinemia, hospitalisations should also be included in the score. Current immunosuppressive drugs including cumulative exposure to steroids may also be important predictors for severe COVID-19 in the presence of comorbidities [9].

Management of comorbidities to reduce risk of severe COVID-19 and death

Management of hypertension, diabetes and coronary artery disease can help in reducing mortality in COVID-19. Currently, there is ample evidence that the use of angiotensin-converting enzyme (ACE) inhibitors and ACE-receptor blockers in patients with hypertension help in reducing both COVID-19 severity and mortality [123]. A good number of meta-analyses have been carried out looking at the effects of renin–angiotensin inhibitors in COVID-19, and now there is sufficient proof that the use of ACE-inhibitors for any indication reduces mortality in COVID-19 [124].

Statins have been shown to be able to reduce cardiovascular mortality in RA [125]. There is a biological basis for statins in reducing atherosclerotic disease in other RMDs like lupus as well [126]. Statins have also been proposed for COVID-19 [127], and there is emerging evidence that statins can reduce mortality in COVID-19. Analysis of hospital data from China has shown that statin treatment was associated with lower mortality (adjusted hazard ratio of 0.63, 95% CI 0.48–0.84, $p = 0.001$) compared to non-statin users [128].

Hydroxychloroquine (HCQS) is a cornerstone drug for lupus and has potential role against atherothrombosis via downregulation of Toll-like receptor signalling, cytokine production, T cell and monocyte activation [129]. Rodent models have demonstrated beneficial effects on endothelial dysfunction [130]. Though not established as a standard of care in vasculitis yet, it has been shown to be helpful in anti-neutrophilic neutrophilic cytoplasmic antibody (ANCA) associated vasculitis, IgA vasculitis, Takayasu's arteritis and polyarteritis nodosa [131]. A significant part of this action may be due to its potential anti-endothelial dysfunction and anti-thrombotic mechanisms in vasculitis. Endothelial dysfunction with 'endotheliitis' plays a significant part in COVID-19 pathogenesis [132]. It has been shown that hydroxychloroquine does not protect from COVID-19 in rheumatology patients [133]. However, higher disease activity in RMDs is independently associated with higher mortality in COVID-19. HCQS should not be stopped in patients already taking them. There is speculation with the demonstration of anti-phospholipid antibodies in COVID-19 patients [134] that these antibodies may have a pathological role. If so, there can be a strong case for HCQS in preventing thrombosis in COVID-19.

Lower vitamin D levels have been associated with more severe COVID-19 [135]. Serum levels of vitamin D have been suggested as a biomarker for outcomes in COVID-19 [136]. The association of mortality with obesity may have low vitamin D as a confounding factor [137]. Many RMDs have low serum vitamin D levels [138]. There is some preliminary evidence of the benefit of vitamin D in RMDs [139]. It needs to be seen whether vitamin D will also help in RMD patients with COVID-19.

Many patients with RMDs receive vitamin D supplementation for osteopenia or osteoporosis. It remains to be seen if this influences the outcomes of COVID-19. One study has shown that people receiving denosumab, zoledronate and duloxetine had a negative association with COVID-19 incidence [140]. This was not true for vitamin D supplementation. It is difficult to interpret the study now and more evidence including the validations of these findings is required.

Maintaining physical health through activity is an essential part of the battle against the pandemic. It is important not to marginalise the benefits of physical activity [137]. Social distancing should not mean any patient has to be isolated at home without any activity like walking. Even staying at home, there is scope for introducing interventions like resistance training, respiratory muscle training (including deep breathing exercises) with aerobics wherever feasible [141]. The breathing exercises described as a part of *Yoga* may help both respiratory muscles as well have short-term favourable outcomes on depression [142].

Effect of COVID-19 on comorbidities in RMDs

There are case reports of several new rheumatic diseases being diagnosed after SARS-CoV-2 infection. Some may be atypical features of COVID-19 itself while others might be simmering RMDs unmasked during the inflammation of COVID-19. However, COVID-19 may itself also initiate autoimmune diseases including RMDs [143]. One immune-mediated syndrome is Multisystem inflammatory syndrome in children (MIS-C) [144]. The inflammatory pathways involved in COVID-19 have remarkable overlap with those of rheumatoid arthritis [145]. However, COVID-19 has not been shown to precipitate arthritis except case reports [146, 147] that are possibly the exceptions that prove the rule. Similarly, there is little evidence to suggest that COVID-19 can worsen pre-existing arthritis [148].

COVID-19 has been shown to precipitate cardiomyopathy, and lung fibrosis had may have more tremendous implications for patients pre-existing RMDs. Magnetic resonance imaging of patients recovered from COVID-19 has shown active cardiac involvement in 60%, independent of pre-existing conditions and severity of COVID-19 [149]. A similar study had also been reported from China [150]. Post-COVID-19 pulmonary fibrosis is likely to be associated with older age, the severity of pneumonia, and background lung disease [151]. Patients with RMDs predisposing to lung pathology may have higher risks of post-COVID-19 fibrosis.

In data from Switzerland, there was no increase in disease activity of RMDs in the short term since the onset of the pandemic. However, drug non-compliance has increased [152]. This might lead to increased flares in the

near future. This can also increase the inflammatory burden and add to cardiovascular risks. Thus, patients with RMDs may have an increased risk of developing comorbidities after exposure to SARS-CoV-2.

Implications for the rheumatologist

The pandemic has forced an unprecedented shift to online platforms and virtual consultations. Now patient-reported outcomes have taken antecedence over physician assessments [153]. However, these will focus more on the primary manifestations of diseases and are likely to relegate comorbidities to the background. Comorbidities, already being sub-optimally managed [2], maybe neglected further. Newer comorbidities may be missed on teleconsultations.

Many drugs used in rheumatology have been proposed for COVID-19 [154]. However, these have not shown any evidence of benefit to date [155]. The small benefit of these drugs may be offset by the presence of the various comorbidities in RMDs. Thus, unless comorbidities are addressed, we may be missing out on much relevant information.

Again, the pandemic may influence drug compliance due to unavailability of drugs, missing appointments with rheumatologists, or even just a fear of using 'immunosuppressant' drugs. This itself might lead to flares and increased comorbidities that might be attributed as a direct pathobiological effect of COVID-19 [156].

Conclusion

Thus, there is a need to stratify RMDs as per the presence and number of comorbidities. This will help physicians predict risk for severe COVID-19 as well as future overall outcomes. It may also have implications on prioritising candidates for future COVID-19 vaccines.

The knowledge about various comorbidities and how to tackle these has expanded in the last couple of decades, but the current pandemic threatens to take the focus away. It is crucial to incorporate protocols to address them during consultations, particularly teleconsultations. Holistic management will only be possible when we focus on the patients as a whole, and not just what is mandated by the primary disease targets.

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Compliance with ethical standards

Conflict of interest The authors have no potential conflicts of interest to disclose.

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