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Original Article

Ruxolitinib and the Mitigation of Severe COVID-19: A Systematic Review and Meta-analysis

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ABSTRACT

Background: The cause of end-organ damage and acute respiratory distress syndrome (ARDS) in coronavirus disease 2019 (COVID-19) patients is postulated to be connected to the uncontrolled increase of pro-inflammatory cytokines. The upregulation of many cytokines is dependent on signaling through the Janus kinase 1 (JAK-1) and JAK-2 pathways. Ruxolitinib, a JAK-1 and JAK-2 inhibitor, is documented to have potent anti-inflammatory activity by targeting several cytokines and growth factors with proposed efficacy in the cytokine storm observed in severe COVID-19 patients; therefore, this study examines the efficacy and tolerability of ruxolitinib for adult COVID-19 patients.
Materials and Methods: This review was conducted using preferred reporting items for aystematic reviews and meta-analyses (PRISMA) methodology. Six reviewers analyzed 1,120 results. Seven studies were selected and validated. A quantitative meta-analysis was further performed to evaluate clinical improvement at day 28, mortality at day 28, and oxygen requirements comparing treatment and standard of care groups.
Results: 168 individuals were involved in the studies selected: 122 in cohort studies, 4 in case reports, and 41 in randomized controlled studies. The ruxolitinib group had a higher likelihood of clinical improvement by the 28th day of treatment when assessed with the standard of care (SOC) group (odds ratio [OR]: 1.48; 95% confidence interval [CI]: 0.53 - 4.16; $P = 0.45$; $I^2 = 0\%$). The SOC group was at a higher risk of experiencing serious adverse events (OR: 0.17; 95% CI: 0.03 - 1.13; $P = 0.07$). Notably the SOC group had a higher likelihood of death (OR: 0.51; 95% CI: 0.11-2.29; $P = 0.07$; $I^2 = 0\%$).
Conclusion: Prior studies on ruxolitinib have demonstrated it is able to decrease inflammatory markers. In recent studies on COVID-19, treatment with ruxolitinib decreased the time on mechanical ventilation, hospitalization time, and the need for vasopressor support. Additionally, ruxolitinib showed decreased mortality and demonstrated improvement in lung congestion as evidenced by computerized tomography imaging. These findings warrant further clinical investigation into Ruxolitinib as a potential treatment approach for severe COVID-19.

Keywords: COVID-19; Ruxolitinib; Cytokine storm; ARDS; JAK-STAT

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INTRODUCTION

The search for therapeutic options against coronavirus disease 2019 (COVID-19) and its associated health consequences continues. With over 202 million cases reported worldwide and fatalities exceeding 4.2 million, the effects of COVID-19 have impacted healthcare globally [1]. COVID-19 has been associated with the uncontrolled production of cytokines known as a cytokine storm, correlated to the severity of the disease [2]. This uncontrolled production of cytokines leads to multi-organ failure and has been associated with increased mortality [3]. Cytokines are released through various mechanisms, including Janus kinase-signal transducer and activator of transcription (JAK-STAT) signaling pathway. The over-activation of this pathway is postulated to induce an exaggerated immune response [4]. Consistently observed with severely ill COVID-19 patients presenting with symptoms of cytokine storm, the upregulation of the JAK-STAT pathway may be managed by JAK-inhibitors [5].

Ruxolitinib is a selective inhibitor of JAK-1 and JAK-2 with varying selectivity against tyrosine kinase 2 (TYK2) and JAK-3 [5]. It is also a vigorous inhibitor of the JAK/STAT signaling pathway partly responsible for viral immunity [6]. It is primarily used to treat myelofibrosis (MF) and polycythemia vera (PV) [7]. Ruxolitinib has also been clinically investigated in the management of graft-versus-host reaction (GvHD) and hemophagocytic lymphohistiocytosis (HLH), diseases also characterized by cytokine release causing unconstrained inflammation [8, 9]. Ruxolitinib can inhibit T-regulatory, dendritic, and natural killer (NK) cells leading to a decrease in the production of inflammatory cytokines such as interleukin-10 (IL-10), interleukin 12 (IL-12), interleukin-23 (IL-23), and transforming growth factor-beta (TGF-β) [6, 10, 11]. IL-12 and IL-23 are responsible for the activation of T helper type 1 (Th1) and T helper type 17 (Th17) cells which then secrete multiple factors including IL-17, IL-22, TNF-α, IFN-γ and IL-2 [6]. Decreasing IL-12 and IL-23 levels may suppress the production of cytokines by deactivating Th-1 and Th-17 cells, ultimately reducing inflammation. This downregulation, however, poses an increased risk of reactivation of latent infections and susceptibility to opportunistic pathogens [6].

The acute respiratory distress syndrome (ARDS) associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has been associated with the activity of viral cytoplasmic nod-like receptor family pyrin domain containing 3 (NLRP3) inflammasome [12]. The activation of NLRP3, along with other factors such as Nuclear Factor Kappa Beta (NF-kβ), macrophages, and Th1 cells, promote the production of pro-inflammatory cytokines; among them, IL-1β and IL-18 causing direct inflammation [12]. Further, the literature also describes the inflammatory role of IL-6 in COVID-19 [13]. Thus, mitigation of the JAK-STAT pathway with pharmacological therapies, such as Ruxolitinib, is postulated to attenuate the pro-inflammatory responses described in patients with COVID-19 [14]. Ruxolitinib has broad anti-inflammatory activity and prior studies have demonstrated its role in the downregulation of cytokine production [15].

We conducted a systematic review to evaluate the duration of hospitalization, supplemental oxygen requirements, rate of intensive care unit (ICU) admission, ICU length of stay, change in national early warning score 2 (NEWS2), systemic inflammatory markers (including C-reactive protein and ferritin), secondary infection rate, and mortality in adult COVID-19 patients treated with Ruxolitinib.

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MATERIALS AND METHODS

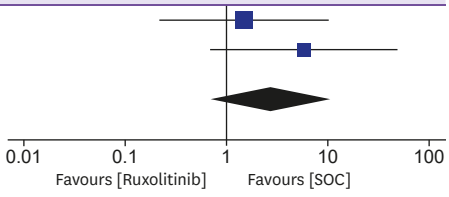
1. Search strategy and study selection

Six reviewers undertook an extensive systematic search of the literature, and a total of 1,120 articles were screened in accordance with the PRISMA guidelines. Databases included PubMed, MEDLINE, Cochrane Library, CINAHL Plus, Embase, and Scopus with no restriction regarding time or language. Grey literature was also reviewed, including Google Scholar and Clinicaltrials.gov. The search for articles was done using keywords, MeSH terms, or synonyms to collect many studies. Various keywords, MeSH terms, synonyms such as COVID-19, ruxolitinib, and INCA 24 combined with Boolean operators or/and were used. There was a total of 44 duplicates which were removed before initial screening. At the initial screening, 1,037 relevant articles were viewed. Eligible studies included case reports, case series, case-control, prospective and retrospective cohort studies, controlled randomized and non-randomized clinical trials, and published and pre-published articles. Commentaries and incomplete or ongoing studies were excluded. Six independent reviewers assessed 83 full-text articles for eligibility, of which 7 studies were included, and any discrepancies were resolved amongst the reviewers. A quantitative meta-analysis was further conducted to evaluate clinical improvement at day 28, mortality at day 28, and oxygen requirements comparing treatment and standard of care groups. The PRISMA flowchart is shown in **Figure 1**.

A

Study or subgroup	Ruxolitinib group Events	Ruxolitinib group Total	SOC group Events	SOC group Total	Weight	Odds ratio M-H, Random, 95% CI
Cao, 2020 (17)	18	20	18	21	55.5%	1.50 (0.22 – 10.08)
Giudice, 2020 (16)	5	7	3	10	44.5%	5.83 (0.70 – 48.87)
Total (95% CI)		**27**		**31**	**100.0%**	**2.75 (0.66 – 11.35)**
Total events	23		21			

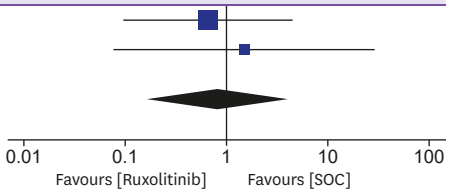
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.87$, df = 1 ($P = 0.35$); $I^2 = 0\%$
Test for overall effect: Z = 1.40 ($P = 0.16$)



B

Study or subgroup	Ruxolitinib group Events	Ruxolitinib group Total	SOC group Events	SOC group Total	Weight	Odds ratio M-H, Random, 95% CI
Cao, 2020 (17)	2	20	3	21	70.7%	0.67 (0.10 – 4.48)
Giudice, 2020 (16)	1	7	1	10	29.3%	1.50 (0.08 – 28.89)
Total (95% CI)		**27**		**31**	**100.0%**	**0.85 (0.17 – 4.19)**
Total events	3		4			

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.20$, df = 1 ($P = 0.65$); $I^2 = 0\%$
Test for overall effect: Z = 0.21 ($P = 0.84$)



C

Study or subgroup	Ruxolitinib group Events	Ruxolitinib group Total	SOC group Events	SOC group Total	Weight	Odds ratio M-H, Random, 95% CI
Cao, 2020 (17)	18	20	18	21	29.3%	1.50 (0.22 – 10.08)
Rosée, 2020 (5)	10	14	66	105	70.7%	1.48 (0.43 – 5.03)
Total (95% CI)		**34**		**126**	**100.0%**	**1.48 (0.53 – 4.16)**
Total events	28		84			

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.00$, df = 1 ($P = 0.99$); $I^2 = 0\%$
Test for overall effect: Z = 0.75 ($P = 0.45$)

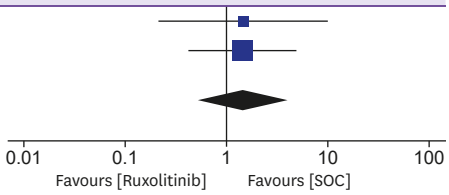


Figure 1. (A) Hospitalization, requiring supplemental oxygen at D1. (B) Hospitalization, requiring high-flow nasal cannula or non-invasive mechanical ventilation at D1. (C) Clinical improvement by D28.
SOC, standard of care; CI, confidence interval.

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2. Quality assessment

Three independent reviewers conducted a quality assessment of the 9 included studies using the Cochrane risk of bias assessment tool for the randomized control studies to assess randomization process, deviation from intended intervention, missing outcome data, measurement of the outcome, and selection of the reported result to determine overall bias. Also, a case report-guidelines checklist was used to evaluate the therapeutic intervention, diagnostic approach, reported outcome, adherence to follow-up, and participant perspective at the level of each included case report. Studies with a 70% or higher score using the quality assessment tools were included in the study; all seven studies had a score greater than 70%.

3. Outcomes

Studies reporting COVID-19 positive patients and control groups (no treatment, treatment according to the hospital guidelines, or National Institutes of Health [NIH] guidelines) were included. Data was tabulated for the observable markers of clinical outcomes including improvement or deterioration of the clinical status by using the NEWS2 score, the mean duration of hospitalization, use of mechanical ventilation, admission to and length of stay in the ICU, laboratory markers for inflammation, secondary infection, and mortality rate.

4. Data analysis

After a careful assessment of included studies in the meta-analysis, quantitative data were entered into a spreadsheet. If more than one study reported data on supplemental oxygen, non-invasive mechanical ventilation, clinical improvement by day 28, any serious adverse events, and/or mortality, the data was meta-analyzed and presented as forest plots using standard effect measures (**Table 1**). Dichotomous data for select values, including the unadjusted odds ratios (ORs), were calculated by applying a random-effects model. A 95% confidence interval (CI) for each measure was hereby presented. The I^2 value was listed to identify any inconsistencies in the study heterogeneity. Review Manager (RevMan) 5.4, a software (Cochrane, London, England) was used to conduct the meta-analysis.

5. Funding source

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. No funding was utilized to conduct this project.

RESULT

168 participants were identified in the studies included. 122 patients from 3 cohort studies, 5 patients from 5 case reports, and 41 patients from 1 randomized controlled trial [5, 16-21]. The participants were men and non-pregnant women aged 31 - 95 years of age (of which 88 (52.4%) were male) with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) positive results by reverse transcriptase-polymerase chain reaction (RT-PCR), except for the randomized control study wherein patients were diagnosed with COVID-19 but only 17 tested positive by RT-PCR. The demographic and underlying medical characteristics of the patients are summarized in **Table 2**.

1. Clinical trial

In the trial conducted by Cao et al., 22 subjects received ruxolitinib while 21 subjects in the control group were given a placebo along with the standard of care [16]. The interventional group clinically improved faster (median: 12; interquartile range [IQR] = 10 - 19) versus

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Table 1. Characteristics of studies included

	Author, Year [Reference No.]	Groups, N	Age	Male, n (%)	NEWS2 score D1	Hospitalization, requiring supplemental oxygen D1, n (%)	Hospitalization, requiring HFNC or non-invasive mechanical ventilation D1, n (%)	Time to clinical improvement (d)	Clinical improvement by D28, n (%)	Mortality, n (%)	Serious adverse events, n (%)
1	Cao, 2020 [17]	20 Ruxolitinib group	63 (51 - 65)	12 (60.0%)	5 (4 - 7)	18 (90.0%)	2 (10.0%)	12 (10 - 19)	18 (90.0%)	0 (0.0%)	0
		21 SOC group	64 (59 - 71)	12 (57.1%)	4 (4 - 5)	18 (85.7%)	3 (14.3%)	15 (10 - 18)	18 (85.7%)	3 (14.3%)	4
2	Giudice, 2020 [16]	7 Ruxolitinib group	61 (53 - 70)	6 (86%)	-	5 (71.4%)	1 (14.3%)	24 (16 - 44)	3 (42.9%)	1 (14.3%)	1
		10 SOC group	63.5 (31 - 85)	7 (70.0%)	-	3 (30.0%)	1 (10.0%)	34 (9 - 60)	NA	1 (10.0%)	4
3	Rosée, 2020 [5]	14 Ruxolitinib sub-group	66 (55 - 81)	11 (79.0%)	8.5 (4 - 16)	2 (14.0%)	11 (79.0%)	18 (9 - 36)	10 (71.4%)	1 (7.1%)	-
		105 SOC group	-	47 (44.8%)	-	-	-	-	66 (63.0%)	12 (11%)	-
4	Koschmieder, 2020 [19]	1 Ruxolitinib group	55	1 (100.0%)	-	1 (100.0%)	-	15	1 (100.0%)	0 (0.0%)	-
5	Saraceni, 2020 [18]	1 Ruxolitinib group	59	1 (100.0%)	-	-	1 (100.0%)	45	0 (0.0%)	0 (0.0%)	-
6	Portsmore, 2020 [20]	1 Ruxolitinib group	74	0	-	-	1 (100.0%)	28	1 (100.0%)	0 (0.0%)	-
		1 Ruxolitinib group	54	1 (100.0%)	-	-	1 (100.0%)	64	0 (0.0%)	0 (0.0%)	-
7	Innes, 2020 [21]	1 Ruxolinitib group	53	1 (100.0%)	-	-	1 (100.0%)	28	1 (100.0%)	0 (0.0%)	-

Values are presented as median interquartile range-unless otherwise specified.
Days of hospitalization, median interquartile range 18.
NEWS2, The National Early Warning Score 2; D1, day 1; SOC, standard of care; HFNC, high-flow nasal cannula; D1, day 1; D28, day 28; NA, non-applicable.

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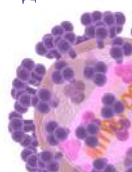

Table 2. Showing baseline demographics and medical conditions in patients

Demographics	
Sample n	168
Ruxolitinib group sample size n (%)	46 (27.4%)
Standard of care group sample size n (%)	122 (72.6%)
Male n (%)	88 (52.4%)
Underlying medical conditions n (%)	
Diabetes mellitus (%)	42 (25%)
Hypertension (%)	93 (55.4%)
Cardiovascular disease (%)	42 (25%)
Chronic lung disease (%)	37 (22.0%)
Current or previous smoker (%)	33 (19.6%)
Graft-versus-host disease	2 (1.2%)

the control group [median = 15; IQR = 10 - 18 days; log-rank test $P = 0.147$; hazard ratio [HR] = 1.669; 95% CI: 0.836 - 3.335]. There was significant improvement observed in the computerized tomography (CT) findings in the intervention group on day 14 (18 [90%] *vs.* 13 [61.9%]; $P = 0.0495$) [17]. The interventional group exhibited clinical improvement on a median day 12, compared to the control group on day 15 [17]. The secondary endpoint was based on suppressing inflammation by ruxolitinib in patients without concomitant corticosteroid treatment [17]. Administration of ruxolitinib 10 mg twice daily and eculizumab 900 mg intravenous (IV) weekly for a maximum of three weeks did not increase the incidence of secondary infection, suggesting that it may not cause significant immunosuppression in this timeframe versus a longer duration of treatment [16]. This composition could potentially be used for the treatment of ARDS related to SARS-CoV-2. Invasive mechanical ventilation or high-flow nasal oxygenation was not required during or after the treatment for any of the patients in this group. By day 28, 3 patients in the control group died of ARDS; the mortality was 14.3% in the control group, in contrast to the ruxolitinib group, where there were no deaths recorded [17]. Other outcomes evaluated the clinical improvement rate: assessment of improvement on days 7, 14, 21, and 28 showed no significant difference; from day 0 until lymphocyte count returned to normal (lymphocyte recovery), patients in the Ruxolitinib group had a significantly shorter median time of recovery from lymphopenia (5 [IQR 2 – 7] days *vs.* 8 [IQR 2 - 11] days; log-rank test $P = 0.033$; HR= 3.307; 95% CI: 1.097 - 8.409) [17]. No significant difference was found from day 0 until invasive mechanical ventilation; four patients in the control group clinically deteriorated, and three required invasive mechanical ventilation in the ICU [17].

2. Cohorts

In the prospective cohort study by Giudice et al., the efficacy of ruxolitinib was examined with a combination of eculizumab and the standardized group receiving the best available treatment (BAT) in moderate to severe ARDS patients [16]. The study reported clinical outcomes for 17 cases that were SARS-CoV-2 positive with associated ARDS (n = 7) with the combined effect of ruxolitinib and eculizumab, and the standardized group receiving the BAT in moderate to severe ARDS patients. Patients that were excluded were individuals that were younger than 17 years of age, individuals that had SARS-CoV-2 negative results, a mild COVID-19 infection, any active infections such as tuberculosis, any clinical conditions in which the use of eculizumab or ruxolitinib is contraindicated, elevated transaminase levels, and/or pregnant or breastfeeding women [16]. The study reported a substantial improvement in the patient's respiratory symptoms and reduced circulating d-dimer concentrations compared to the BAT group [16]. Clinical improvement was noticed three days after the addition of ruxolitinib, in contrast with seven days in the BAT group. A

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significant improvement in PaO2 and PaO2/FiO2 ratio was also reported with Ruxolitinib compared to the BAT group ($P = 0.0260$ and $P = 0.0395$, respectively) [16]. CT findings showed improvements based on decreased ground glass appearance, resolving pneumonitis, and reduction in the opacities and consolidation similar to Cao et al. [16, 17]. Giudice et al. reported one death in the ruxolitinib treatment group [16]. The patient had a history of non-Hodgkin's lymphoma (NHL) and developed severe symptoms of COVID-19. The presence of NHL may have contributed to the severity of the disease and mortality [16].

La Rosée et al. conducted a retrospective study and reported one death out of 14 patients in the treatment arm [5]. The study reported clinical improvement in 11 out of 14 patients. These 14 patients had a COVID-19 inflammation score (CIS) greater than or equal to 10 out of 16 points and were initially administered 7.5 mg ruxolitinib twice daily. The dose increased until a cumulative dose of 135 mg was given over a median of 9 days [5]. The clinical assessment was performed using a seven ordinal category scale system where 11 out of the 14 patients scored a 5, which meant they were hospitalized while on non-invasive ventilation []). A dose of 7.5 mg of ruxolitinib given twice daily led to a reduction of CIS by 25% in 9 of the 14 patients seen on days 5 and 7 [5]. Of the 105 patients hospitalized for COVID-19, 66 (63%) patients improved without any additional therapy and only by standard of care (SOC) treatment. A total of 27 (25.7%) deteriorated and were assessed to have a high risk for hyper-inflammation, according to CIS [5]. Of 14 patients who received ruxolitinib, the median NEWS2 score at baseline was 8.5 [5], demonstrating the high risk of severe disease in these patients [5]. All 14 patients in the ruxolitinib treatment group presented with a CIS score greater than 10 out of 16 points and had radiological signs consistent with bilateral COVID-19 associated ARDS or COVID-19 pneumonitis [5]. Only 1 patient receiving ruxolitinib died, whereas 10 recovered entirely [5].

Capochiani et al., conducted a retrospective cohort study where clinical data was collected on 18 patients who tested positive for COVID-19. Out of the 18 patients, 67% were male (12 out of 18), and 33% were female (6 out 18) (22). This study also comprised 33% chronically ill patients with comorbidities documented prior to their COVID-19 diagnosis [22]. Furthermore, all of the patients had rapidly progressive ARDS and were started on 20 mg of ruxolitinib within 4 to 15 days of initial COVID-19 symptoms. The patients had a PaO2/FiO2 ratio of 106 to 208 on non-invasive ventilation (NIV) and were all eligible for mechanical ventilation per set guidelines [22]. The study reported that 16 patients showed improvements within 48 hours of treatment with ruxolitinib, and at 14 days, experienced full recovery of respiratory function. Laboratory findings were not correlated to treatment response. The only exception was of IL-6's normal (less than 12.7) to high levels (greater than 12.7), which had a significant correlation to time of onset of symptoms (approximately 10 days) [22]. 16 out of 18 patients had a decrease in IL-6 and did not progress from NIV to invasive mechanical ventilation. There was a complete overall response rate (ORR) of 89% [22]. While the observational study was ongoing with the initial 18 patients, 33 other patients who tested positive for COVID-19 and who presented with severe ARDS were not given ruxolitinib as a treatment. In contrast to the 18 study subjects, 19 out of the 33 patients had deteriorating respiratory failure requiring progression from NIV to mechanical ventilation, and 9 patients passed away [22].

3. Dosing and tolerability

In the above studies, the patients received varying dosages of the trial medication. As reported by Cao et al., 20 out of 41 patients who received oral ruxolitinib 5 mg twice per day

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showed median clinical improvement in 12 days [17]. In the study by Giudice et al., patients who were administered combination therapy, including ruxolitinib (10 mg twice daily for 14 days) and eculizumab (900 mg intravenously each week for three weeks) clinically improved within three days [16]. More extensive randomized trials are required to provide conclusive evidence on the most effective dosages needed for better clinical outcomes.

In the study by Cao et al, 16 patients in the ruxolitinib treatment group self-reported adverse effects. One patient progressed to grade-3 lymphocytopenia which improved within two days without discontinuing ruxolitinib [17]. In the same trial, another patient developed grade three hypertension; however, this was transient and resolved [17]. Similarly, La Rosée et al. described two patients who progressed to grade 3 anemia [5]. According to Cao et al., anemia was the most common adverse event in the treatment group and was classified as mild to moderate anemia [17]. No serious or life-threatening adverse events or anaphylaxis were detected or reported in the treatment group, indicating a relatively safe profile.

The administration of ruxolitinib varied significantly per study. The dose of ruxolitinib ranged from 7.5 mg to 15 mg twice daily in one retrospective study conducted by Rose et al. The dosage was dependent on the daily follow-up of efficacy and toxicity for a stepwise dosage increase (15 mg, 0 mg, 7.5 mg; 15 mg, 0 mg, 15 mg) at days 3, 5, or 7 [5]. In another study conducted by Giudice et al., seven of 17 patients received 10 mg twice daily for 14 days [16]. Lastly, in the study by Cao et al., the patients enrolled in the ruxolitinib treatment group were administered a dose of 5 mg twice a day for 28 days [17]. All patients who were not treated with ruxolitinib received the best available therapy, which varied per trial site. Outcomes were different in each study, ranging from ruxolitinib having drug-induced liver toxicity to bone marrow dysfunction. Furthermore, COVID-19 patients with latent tuberculosis infection that were administered ruxolitinib had no evident signs of toxicity or tuberculosis reactivation.

According to Capochiani et al., after administering 20 mg of ruxolitinib twice daily, a de-escalation of the treatment was followed. 10 mg was given twice daily for 3 days, and 5 mg was given twice daily for two days respectively for a total of 1 week of treatment [22].

4. Case Reports

Five case reports outlined the clinical course of six patients who received ruxolitinib. One report identified a 74-year-old female with high-grade B-cell lymphoma (BCL) and a 54-year-old male with COVID-19 symptoms admitted to the hospital. Both patients demonstrated clinical improvement when tocilizumab was co-administered with ruxolitinib [20]. One patient exhibited severe symptoms that were refractory to tocilizumab, and continued deterioration prompted the administration of ruxolitinib [20]. Similarly, a patient with chronic GvHD who presented with fatigue, dry cough, and mild dyspnea showed clinical improvement after receiving ruxolitinib. The PaO2/FiO2 ratio progressively increased from 141 on day 10 to 380 on day 31 in patients that received ruxolitinib [18]. Two studies described the dosing of ruxolitinib at 5 - 10 mg twice daily [18, 21]. In the study conducted by Portsmore et al., two patients received combination therapy with ruxolitinib and tocilizumab [20]. Across the case reports examined, four of the five patients had severe disease; one patient had a mild case and was receiving ruxolitinib prior to diagnosis of COVID-19 for pre-existing primary MF [19].

Of the five patients that were diagnosed with COVID-19 and received ruxolitinib, throat swabs from two patients were positive for SARS-CoV-2 by PCR. Both cases had significant underlying

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comorbidities, including chronic myeloid leukemia (CML), secondary hemophagocytic lymphohistiocytosis (sHLH), high-grade BCL, MF, chronic kidney disease (CKD), NHL, arterial hypertension, type II diabetes mellitus (Type 2 DM), and obesity. Three of the patients had a history of transplant, and one had a history of GvHD [18-20]. One of the patients had been receiving ruxolitinib for 15 months before being diagnosed with COVID-19 and did not require mechanical ventilation [19]. The other four patients required mechanical ventilation including continuous positive airway pressure (CPAP) during their hospital stay [18, 20, 21]. Two of the patients received combined therapy consisting of ruxolitinib and tocilizumab, while a third patient initially received tocilizumab but was refractory to it and was switched to ruxolitinib [20, 21]. The fourth patient received ruxolitinib, and the dose of ruxolitinib ranged from 5mg twice daily to 10mg twice daily [18].

Sammartano et al presents a case report of a 59-year-old male afflicted with blastic plasmacytoid dendritic cell neoplasm (BPDCN). The patient was on a multi-chemotherapy regimen which included hyper-CVAD (Hyperfractionated, Cyclophosphamide, Vincristine, Adriamycin and Dexamethasone) who developed ARDS related to COVID-19. His symptoms worsened as treatment with azithromycin, hydroxychloroquine, corticosteroids, and tocilizumab began to fail. The patient subsequently suffered respiratory failure and required mechanical ventilation. Ruxolitinib was administered at 20 mg twice daily. There were signs of rapid clinical and radiological improvement in the patient's respiratory function. Of note, there was significant improvement following the 4th dose. The dose was deescalated and withdrawn after a total treatment of seven days. The patient recovered completely, and had a negative PCR for COVID-19 three weeks later without any reported adverse effects [23].

5. Quantitative findings

Two of the 3 studies [16, 17] reported data of patients requiring supplemental oxygen, High-flow nasal cannula (HFNC) and/or non-invasive mechanical ventilation at baseline (**Fig. 1**). As compared to the SOC group, the Ruxolitinib group had a higher requirement of supplemental oxygen (OR: 2.75; 95% CI: 0.66 - 11.35; $P = 0.16$; $I^2 = 0\%$) (**Fig. 1A**). The ruxolitinib group had a less likelihood of requiring HFNC or non-invasive mechanical ventilation at baseline as compared to the SOC group (OR: 0.85; 95% CI: 0.17 - 4.19; $P = 0.84$; $I^2 = 0\%$) (**Fig. 1B**). The studies used standard oxygenation and ventilation COVID-19 treatment guidelines as laid out by the NIH. Two of the three studies [5, 17] presented clinical improvement by day 28. A central outcome of interest for this meta-analysis was the clinical improvement from the start of treatment, based on the World Health Organization severity score point increase during hospitalization during follow-up, until the 28-day period. As compared to the SOC group, the ruxolitinib group had a higher likelihood of clinical improvement by the 28th day of treatment (OR: 1.48; 95% CI: 0.53 - 4.16; $P = 0.45$; $I^2 = 0\%$) (**Fig. 1C**). There was no heterogeneity in the studies.

Two of the 3 studies reported data of patients requiring supplemental oxygen, HFNC/non-invasive mechanical ventilation at baseline (**Fig. 1**). As compared to the SOC group, the Ruxolitinib group had a higher requirement of supplemental oxygen (OR: 2.75; 95% CI: 0.66 - 11.35; $P = 0.16$; $I^2 = 0\%$) (**Fig. 1A**). The Ruxolitinib group had a less likelihood of requiring HFNC or non-invasive mechanical ventilation at baseline as compared to the SOC group (OR: 0.85; 95% CI: 0.17 - 4.19; $P = 0.84$; $I^2 = 0\%$) (**Fig. 1B**). Two of the three studies presented clinical improvement by day 28. As compared to the SOC group, the Ruxolitinib group had a higher likelihood of clinical improvement by the 28th day of treatment (OR: 1.48; 95% CI: 0.53 - 4.16; $P = 0.45$; $I^2=0\%$) (**Fig. 1C**). There was no heterogeneity in the studies.

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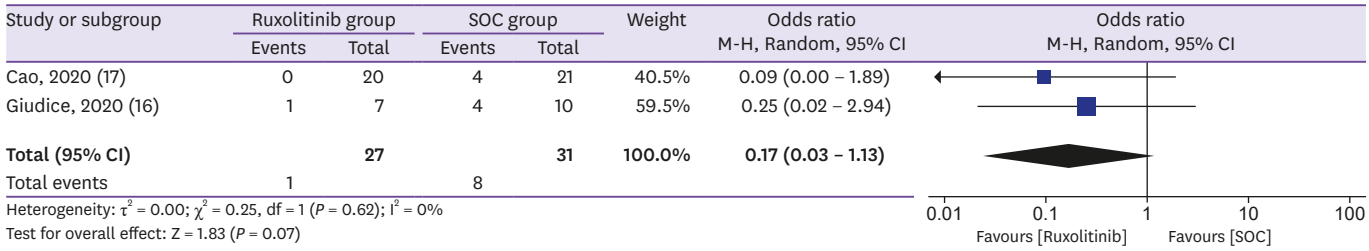

Figure 2. Serious adverse events post initiation of treatment.

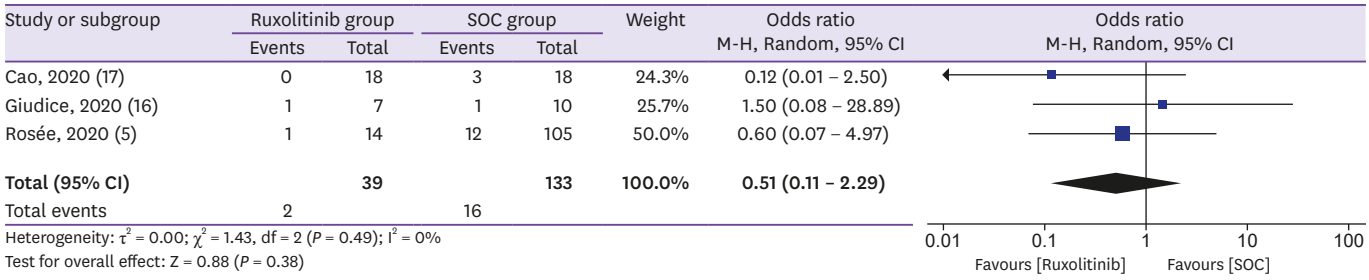

Figure 3. Mortality outcomes in treated and controlled groups.

1) Serious adverse events post initiation of treatment.
Two of the three studies evaluated treatment and control groups for any serious adverse events. As compared to the ruxolitinib group, the SOC group was at a higher risk of contracting serious adverse events (OR: 0.17; 95% CI: 0.03 - 1.13; $P = 0.07$) (**Fig. 2**). There was no heterogeneity in the included studies (I^2=0%).

2) Mortality outcomes in treated and controlled groups.
Three of the 3 studies reported data on mortality outcomes in the ruxolitinib and SOC group. As compared to the ruxolitinib group, the SOC group had a higher likelihood of death (OR: 0.51; 95% CI: 0.11 - 2.29; $P = 0.07$; I^2=0%) (**Fig. 3**).

DISCUSSION

Our systematic review indicates that patients treated with ruxolitinib showed overall improvement in clinical symptoms, CT imaging findings, reduced length of hospital stay, and no severe adverse events when given for a 12-week period or less. Simultaneously, the failure to provide evidence on patients' extended follow-up for their risk for adverse events and smaller size of the available studies needs to be justified. Overall, ruxolitinib showed improved mortality and morbidity in severely ill COVID-19 patients when other treatment options failed to render any clinical benefit. Observed explicitly in the quantitative synthesis, ruxolitinib had a reduced likelihood of HFNC or non-invasive mechanical ventilation at baseline. Additionally, there was significant clinical improvement in the ruxolitinib group on day 28 after initiation of treatment. ruxolitinib was associated with half the likelihood of mortality when compared with the standard of care management alone.

The case reports identified clinical improvement evidenced by successful weaning of mechanical ventilation, normalization of inflammatory markers (*i.e.*, C-reactive protein and ferritin), and subsequent hospital discharge. There was also a decline in the H-score, which

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calculates the probability of sHLH, from 214 to 185 [20]. In comparison with the included randomized control trial and cohort studies, participants showed clinical improvement with ruxolitinib, evidenced by a significantly shorter median time of recovery from lymphopenia, improved CT findings, higher PaO2 and PaO2/FiO2 ratio, and decreased d-dimer levels [16].

At this time, it is difficult to ascertain whether the observed clinical improvement can be attributed solely to ruxolitinib. However, having obtained evidence in which clinical improvement with Ruxolitinib is noted, this warrants further investigation into its application in the treatment of COVID-19 patients.

Our study has significant limitations; much of them inherent to the design and methods of the included studies. Though the studies eligible were conducted in different parts of the world, including China, Germany, Italy, and the UK, the population studied is confined to these places and hence does not represent the general population globally as their country-specific factors differ from other countries. These may include genetic variability in patients, strains of SARS-CoV-2 infection, nutritional status among other factors, and thereby their response to treatment. In some case report studies, patients had severe comorbid conditions. Such patients might experience severe COVID-19 symptoms due to underlying health status, unlike the general population with COVID-19. Additionally, there are fewer publications regarding the use of ruxolitinib for SARS-Cov2, therefore, this might be reflected as a lower power study.

The majority of the studies included in this review have a moderate risk of bias. This analysis was primarily driven by the potential for selection bias due to the smaller sample size. The results of two cohort studies and the randomized controlled clinical trial suggesting safety and efficacy with ruxolitinib are reliable due to their low risk of selection bias, reporting bias, performance bias, detection bias, attrition bias, and other biases but cannot be generalized due to its smaller sample size. Further trials should be conducted to prove the safety, incidence, and characterization of adverse events, and clinical outcomes if given for a longer duration of treatment (more than 12 weeks). While the drug was shown to be efficient and safe within these parameters, further multi-center, blinded randomized controlled trials are required to prove its benefit in larger populations and with a longer duration of therapy.

In conclusion, based on our findings, we conclude that the benefits of ruxolitinib in addition to its relatively tolerable safety profile make it a candidate for further investigation as a therapeutic option for the treatment of COVID-19 in adult patients. As more information becomes available and larger clinical trials are conducted, ruxolitinib could emerge as a valuable asset in the arsenal of therapies to treat COVID-19.

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SUPPLEMENTARY MATERIAL

Supplementary Figure 1

PRISMA flowchart.

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