CQ1. 코로나19 환자에게 remdesivir 투여가 표준치료 혹은 무처치 대조군에 비하여 치료효과 및 안전성이 있는가? [RCT]

선행가이드라인 표시	문헌번호	1저자 (출판연도)	연구유형	대상자 (N)	중재군(N)	비교/대조군 (N)	연구결과	결론	Quality Assessment (ROB)								Primary outcomes
									Randomization	allocation concealment	blinding of participants and personnel	blinding of outcome assessment	incomplete outcome data	selective outcome data		certainty of evidence	
WHO living guideline 20 Nov 2020		WHO Therapeutics and COVID-19 (2020)	Systematic review and network meta-analysis	All (7346)	3838	3508	Remdesivir has possibly no effect on mortality (odds ratio 0.90, 95% confidence interval [CI] 0.70 - 1.12; absolute effect estimate 10 fewer deaths per 1000 patients, 95% CI from 29 fewer - 11 more deaths per 1000 patients; low certainty evidence); and possibly no effect on the other important outcomes identified by the panel, with similar low to very low certainty of evidence.	This living WHO guideline on therapeutics for COVID-19 now includes a conditional recommendation against the use of remdesivir, triggered by results from the WHO SOLIDARITY trial	Low	Low	Low	Low	High	High			
WHO, ACPG, NIH, IDSA	#42	Biegel, ACTT-1 (2020) NCT04280705	RCT	Mild to severe (1062)	541	521	Patients who received remdesivir had a median recovery time of 10 days (95% confidence interval [CI], 9 to 11), as compared with 15 days (95% CI, 13 to 18) among those who received placebo (rate ratio for recovery, 1.29; 95% CI, 1.12 to 1.49; P<0.001, by a log-rank test). In an analysis that used a proportional-odds model with an eight-category ordinal scale, the patients who received remdesivir were found to be more likely than those who received placebo to have clinical improvement at day 15 (odds ratio, 1.5; 95% CI, 1.2 to 1.9, after adjustment for actual disease severity). The Kaplan–Meier estimates of mortality were 6.7% with remdesivir and 11.9% with placebo by day 15 and 11.4% with remdesivir and 15.2% with placebo by day 29 (hazard ratio, 0.73; 95% CI, 0.52 to 1.03). Serious adverse events were reported in 131 of the 532 patients who received remdesivir (24.6%) and in 163 of the 516 patients who received placebo (31.6%)	Remdesivir was superior to placebo in shortening the time to recovery in adults who were hospitalized with Covid-19 and had evidence of lower respiratory tract infection.	Low	Low	Low	Low	High	High		High	Time to recovery, defined as the first day, during the 28 days after enrollment, on which a patient satisfied categories 1, 2, or 3 on the eight-category ordinal scale
WHO	#562	Spinner, SIMPLE MODERATE NCT04292730	RCT	Moderate (596)	10-day course (n = 197), 5-day course (n = 199)	200	Patients in the 5-day remdesivir group had statistically significantly higher odds of a better clinical status distribution than those receiving standard care (odds ratio, 1.65; 95%CI, 1.09-2.48; P = .02) on day 11. The clinical status distribution on day 11 between the 10-day remdesivir and standard care groups was not significantly different (P = .18 by Wilcoxon rank sum test). By day 28, 9 patients had died: 2 (1%) in the 5-day remdesivir group, 3 (2%) in the 10-day remdesivir group, and 4 (2%) in the standard care group. Nausea (10% vs 3%), hypokalemia (6%vs 2%), and headache (5%vs 3%) were more frequent among remdesivir-treated patients compared with standard care.	Among patients with moderate COVID-19, those randomized to a 10-day course of remdesivir did not have a statistically significant difference in clinical status compared with standard care at 11 days after initiation of treatment. Patients randomized to a 5-day course of remdesivir had a statistically significant difference in clinical status compared with standard care, but the difference was of uncertain clinical importance.	Yes	Yes	Yes	Yes	No	No	18-Apr-20	High	Clinical status assessed by a 7-point ordinal scale on Day 11
WHO, ACPG		Pan, SOLIDARITY ISRCTN83971151	RCT	Mild-to-severe (5451)	2743	2708	In 405 hospitals in 30 countries 11,266 adults were randomized, with 2750 allocated Remdesivir, and 4088 no study drug. 1253 deaths were reported (at median day 8, IQR 4-14). Kaplan-Meier 28-day mortality was 12% (39% if already ventilated at randomization, 10% otherwise). Death rate ratios (with 95% CIs and numbers dead/randomized, each drug vs its control) were: Remdesivir RR=0.95 (0.81-1.11, p=0.50; 301/2743 active vs 303/2708 control). Remdeisvir did not definitely reduced mortality (in unventilated patients or any other subgroup of entry characteristics), initiation of ventilation or hospitalisation duration.	Remdesivir appeared to have little or no effect on hospitalized COVID-19, as indicated by overall mortality, initiation of ventilation and duration of hospital stay.	Low	Low	Low	Low	High	High		High	In-hospital mortality not only in all patients but also in those with moderate COVID and in those with severe COVID
WHO		Wang (2020) NCT04257656	RCT	Severe (237)	158	79	Remdesivir use was not associated with a difference in time to clinical improvement (hazard ratio 1·23 [95% CI 0·87–1·75]). Although not statistically significant, patients receiving remdesivir had a numerically faster time to clinical improvement than those receiving placebo among patients with symptom duration of 10 days or less (hazard ratio 1·52 [0·95–2·43]). Adverse events were reported in 102 (66%) of 155 remdesivir recipients versus 50 (64%) of 78 placebo recipients. Remdesivir was stopped early because of adverse events in 18 (12%) patients versus four (5%) patients who stopped placebo early	Remdesivir was not associated with statistically significant clinical benefits. However, the numerical reduction in time to clinical improvement in those treated earlier requires confirmation in larger studies	Low	Low	Low	Low	Low	High		Low	Time to clinical improvement within 28 days after randomisation

CQ1. 코로나19 환자에게 remdesivir 투여가 표준치료 혹은 무처치 대조군에 비하여 치료효과 및 안전성이 있는가? [non-RCT]

문헌 번호	1저자 (출판연도)	연구유형	대상자 (N)	중재군(N)	비교/대조군 (N)	연구결과	결론	Quality Assessment (RoBANS)							
								대상자비교 가능성	대상자 선정	교란변수	노출측정	평가자의 눈가림	결과평가	불완전한 결과자료	선택적 결과보고
#373	Pasquini (2020)	Retrospective cohort study; compassionate use of remdesivir	Paitents under MV (51)	25	26	Kaplan–Meier curves showed significantly lower mortality among patients who had been treated with remdesivir (56% versus 92%, P < 0.001). Cox regression analysis showed that the Charlson Comorbidity Index was the only factor that had a significant association with higher mortality (OR 1.184; 95% CI 1.027–1.365; P = 0.020), while the use of remdesivir was associated with better survival (OR 3.506; 95% CI 1.768–6.954; P < 0.001)	In this study the mortality rate of patients with COVID-19 under mechanical ventilation is confirmed to be high. The use of remdesivir was associated with a significant beneficial effect on survival	low	low	low	unclear	unclear	low	low	low
#407	Rivera (2020)	Retrospective cohort study	Cancer patients with mild-to-severe severitie s (2186)	Alone or in combination: hydroxychloroquine (n = 538, 25%), azithromycin (n = 485, 22%), **remdesivir (n = 124, 6%**), high-dose corticosteroids (n = 109, 5%), tocilizumab (n = 94, 4%), and other therapy (n = 90, 4%)	No treatment (n=1,321, 60%	Remdesivir had numerically reduced mortality versus untreated controls that did not reach statistical signifi cance. Baseline COVID-19 severity was strongly associated with receipt of any treatment.	Evaluating the potential role of COVID-19 treatments in patients with cancer in a large observational study, there was no statistically signifi cant 30-day all-cause mortality benefi t with hydroxychloroquine or high-dose corticosteroids alone or in combination; remdesivir showed potential benefit.	high	high	high	unclear	unclear	low	low	low
#491	Olender 2020	Randomized open-label trial (NCT04292899 and EUPAS34303)	Severe (1130)	312	818	At day 14, 74.4% of patients in the remdesivir-cohort had recovered versus 59.0% in the non-remdesivir-cohort (adjusted odds ratio [aOR] 2.03: 95% confidence interval [CI]: 1.34–3.08, P < .001). At day 14, 7.6% of patients in the remdesivir-cohort had died versus 12.5% in the non-remdesivir-cohort (aOR 0.38, 95% CI: .22–.68, P = .001)	In this comparative analysis, by day 14, remdesivir was associated with significantly greater recovery and 62% reduced odds of death versus standard-of-care treatment in patients with severe COVID-19	low	low	high	unclear	unclear	high	low	low
#211	Kalligeros 2020	Retrospective cohort study, combined with multicenter, open-label clinical trial (NCT04292899)	Severe (224)	99	125	The unadjusted risk for 28-day in-hospital death was lower for patients who received remdesivir compared with patients who received supportive care (hazard ratio [HR], 0.42; 95% CI, 0.16–1.08). Although this trend remained the same after adjusting for age, sex, race, and oxygen requirements on admission (adjusted HR [aHR], 0.49; 95% CI, 0.19–1.28), as well as chronic comorbidities and use of corticosteroids (aHR, 0.44; 95% CI, 0.16–1.23), it did not reach statistical significance. The use of remdesivir was not associated with an increased risk of acute kidney injury (AKI) or liver test abnormalities. Although not statistically significant, the rate ratios for time to recovery, clinical improvement, and discharge were higher in women and black or African American patients	Patients on remdesivir had lower, albeit not significant, all-cause in-hospital mortality, and the use of remdesivir did not increase the risk for AKI.	low	high	high	high	unclear	high	low	low

CQ2. 코로나 19 환자에게 hydroxychloroquine 혹은 hydroxychloroquine과 azithromycin 병합 투여가 도움이 되는가? [RCT]

선행가이드라인 표시	문헌번호	1저자 (출판연도)	연구유형	대상자 (N)	중재군(N)	비교/대조군 (N)	연구결과	결론	Quality Assessment (ROB)							certainty of evidence
									Randomization	allocation concealment	blinding of participants and personnel	blinding of outcome assessment	incomplete outcome data	selective outcome data		
ACPG	50	WHO solidarity consortium (2020)	open label, multi-center	11266	HCQ = 954	standard of care = 906	[1] Death rate ratios were Hydroxychloroquine risk ratio 1.19 (0.89~1.59, p=0.23; 104/947 vs 84/906) [2] The pre-planned study outcomes were death, ventilation and time to discharge. No study drug appreciably reduced initiation of ventilation in those not already ventilated. The numbers, study drug vs control, with ventilation initiated after randomization were: Hydroxychloroquine 75 vs 66 [3] The proportions still hospitalized at day 7, study drug vs control, were Hydroxychloroquine 64%v54%. [3] All active treatment ended within ≤14 days, and the numbers of deaths during this 14-day period with any cardiac cause mentioned on the electronic death record was Hydroxychloroquine 4 vs 2.	For Hydroxychloroquine, Solidarity found no definite evidence of benefit or of hazard in any subgroup.	Yes	No	No	No	No	Yes	2020.10.15/2020.12.2	High
	55	Chen J (2020)	Randomized, controlled	60	HCQ= 30	30	[1] One patient in HCQ group developed to severe during the treatment. [2] On day 7, nucleic acid of throat swabs was negative in 13 (86.7%) cases in the HCQ group and 14 (93.3%) cases in the control group (P>0.05). [3] The median duration from hospitalization to virus nucleic acid negative conservation was 4 (1, 9) days in HCQ group, which is comparable to that in the control group [2 (1, 4) days, Z=1.27, P>0.05]. [4] The median time for body temperature normalization in HCQ group was 1 (0, 2) day after hospitalization, which was also comparable to that in the control group [1 (0, 3) day]. [5] Radiological progression was shown on CT images in 5 cases (33.3%) of the HCQ group and 7 cases (46.7%) of the control group, and all patients showed improvement in follow-up examinations. [6] Four cases (26.7%) of the HCQ group and 3 cases (20%) of the control group had transient diarrhea and abnormal liver function (P>0.05).	Larger sample size study are needed to investigate the effects of HCQ in the treatment of COVID-19.	Yes	No	No	No	Yes	No	2020.3.6	High
	56	Chen Z (2020)	Randomized, controlled, blind, single center	62	HCQ = 31	31	[1] No difference in the age and sex distribution between the control group and the HCQ group. [2] But for TTCR, the body temperature recovery time and the cough remission time were significantly shortened in the HCQ treatment group. [3] Besides, a larger proportion of patients with improved pneumonia in the HCQ treatment group (80.6%, 25 of 31) compared with the control group (54.8%, 17 of 31).	Among patients with COVID-19, the use of HCQ could significantly shorten TTCR and promote the absorption of pneumonia.	Yes	Yes	Yes	Yes	No	Yes	2020.4.10	moderate d/t serious risk of bias
	59	Tang (2020)	Multi-center, open label, randomized, controlled	159	HCQ=75	75	[1] The negative conversion probability by 28 days in SOC plus HCQ group was 85.4% (95% confidence interval (CI) 73.8% to 93.8%), similar to that in the SOC group 81.3% (95%CI 71.2% to 89.6%). [2] Between-group difference was 4.1% (95%CI -10.3% to 18.5%).	The administration of HCQ did not result in a significantly higher negative conversion probability than SOC alone in patients mainly hospitalized with persistent mild to moderate COVID-19.	Yes	No	No	No	No	Yes	2020.5.7	High
	64	Chen L (2020)	open label, randomized, single center	48	CQ = 18, HCQ= 18	12	[1] The chloroquine group achieved shorter time to clinical recovery (TTCR) than the control group (P=0.019). [2] There was a trend toward reduced TTCR in the hydroxychloroquine group (P=0.049). [3] The time to reach viral RNA negativity was significantly faster in the chloroquine group and the hydroxychloroquine group than in the control group (P=0.006 and P=0.010, respectively). [4] The median numbers of days to reach RNA negativity in the chloroquine, hydroxychloroquine, and control groups was 2.5 (IQR: 2.0-3.8) days, 2.0 (IQR: 2.0-3.5) days, and 7.0 (IQR: 3.0-10.0) days, respectively. [5] The chloroquine and hydroxychloroquine groups also showed trends toward improvement in the duration of hospitalization and findings on lung computerized tomography (CT).	This study provides evidence that (hydroxy)chloroquine may be used effectively in treating moderate COVID-19 and supports larger trials.	Yes	No	No	No	No	Yes	2020.6.22	high
	66	Mitja O (2020)	a multicenter, open label, randomized controlled trial	293	157	136	[1] No significant differences were found in the mean reduction of viral load at day 3 (-1.41 vs. -1.41 Log10 copies/mL in the control and intervention arm, respectively; difference 0.01 [95% CI -0.28;0.29]) or at day 7 (-3.37 vs. -3.44; d -0.07 [-0.44;0.29]). [2] This treatment regimen did not reduce risk of hospitalization (7.1%, control vs. 5.9%, intervention; RR 0.75 [0.32;1.77]) nor shortened the time to complete resolution of symptoms (12 days, control vs. 10 days, intervention; p = 0.38).	In patients with mild Covid-19, no benefit was observed with HCQ beyond the usual care.	Yes	N0	No	No	No	Yes	2020.7.16	High

	67	Skipper CP (2020)	Multi center, randomized, double-blind, placebo-controlled trial	491	HCQ= 244	247	[1] Change in symptom severity over 14 days did not differ between the hydroxychloroquine and placebo groups (difference in symptom severity: relative, 12%; absolute, -0.27 point [95% CI, -0.61 to 0.07 point]; P = 0.117). [2] At 14 days, 24% (49 of 201) of participants receiving hydroxychloroquine had ongoing symptoms compared with 30% (59 of 194) receiving placebo (P = 0.21).	Hydroxychloroquine did not substantially reduce symptom severity in outpatients with early, mild COVID-19	Yes	Yes	Yes	Yes	No	Yes	2020.7.16	High
	68	Chen C-P (2020)	multi center, randomized controlled trial and retrospective study	RCT : 33, retrospective study : 37	21	12	[1] In the RCT, the median times to negative rRT-PCR from randomization to hospital day 14 were 5 days (95% CI; 1-9 days) and 10 days (95% CI; 2-12 days) for the HCQ and SOC groups, respectively (p = 0.40). [2] On day 14, 81.0% (17/21) and 75.0% (9/12) of the subjects in the HCQ and SOC groups, respectively, had undetected virus (p = 0.36). In the retrospective study, 12 (42.9%) in the HCQ group and 5 (55.6%) in the control group had negative rRT-PCR results on hospital day 14 (p = 0.70).	Neither study demonstrated that HCQ shortened viral shedding in mild to moderate COVID-19 subjects.	Yes	No	No	No	No	Yes	2020.7.10	low
	7+B12:Q123	Cavalcanti AB (2020)	a multicenter, randomized, open-label, three-group, controlled trial	467	HCQ + AZ : 217, HCQ : 221	227	[1] As compared with standard care, the proportional odds of having a higher score on the seven-point ordinal scale at 15 days was not affected by either hydroxychloroquine alone (odds ratio, 1.21; 95% confidence interval [CI], 0.69 to 2.11; P=1.00) or hydroxychloroquine plus azithromycin (odds ratio, 0.99; 95% CI, 0.57 to 1.73; P=1.00). [2] Prolongation of the corrected QT interval and elevation of liver-enzyme levels were more frequent in patients receiving hydroxychloroquine, alone or with azithromycin, than in those who were not receiving either agent.	Among patients hospitalized with mild-to-moderate Covid-19, the use of hydroxychloroquine, alone or with azithromycin, did not improve clinical status at 15 days as compared with standard care.	Yes	No	No	No	No	Yes	2020.7.23	High
	75	Abd-Elsalam S (2020)	multicenter, randomized cor	194	HCQ : 97	97	[1] The overall mortality did not differ between the two groups, as six patients (6.2%) died in the HCQ group and 5 (5.2%) died in the control group (P = 0.77). [2] Univariate logistic regression analysis showed that HCQ treatment was not significantly associated with decreased mortality in COVID-19 patients.	Adding HCQ to standard care did not add significant benefit, did not decrease the need for ventilation, and did not reduce mortality rates in COVID-19 patients.	Yes	No	No	No	No	Yes	2020.10.1	High
	76	Lyngbakken MN (2020)	single, open-label, randomized, controlled trial	53	HCQ : 27	26	Treatment with hydroxychloroquine did not result in a significantly greater rate of decline in SARS-CoV-2 oropharyngeal viral load compared to standard care alone during the first five days.	Our results suggest no important antiviral effect of hydroxychloroquine in humans infected with SARS-CoV-2.	Yes	No	No	No	No	Yes	2020.7	moderated/t serious risk of bias
	78	Ulrich R (2020)	a multicenter, double-blind randomized trial	128	HCQ : 67	61	[1] There were no significant differences in COVID-19 clinical scores, number of oxygen-free days, SARS-CoV-2 clearance, or adverse events between HCQ and placebo. [2] HCQ was associated with a slight increase in mean corrected QT interval, an increased D-dimer, and a trend toward an increased length of stay.	In hospitalized patients with COVID-19, our data suggest that HCQ does not prevent severe outcomes or improve clinical scores.	Yes	Yes	Yes	Yes	No	Yes	2020.9.23	High
	79	RECOVERY Collaborative Group (2020)	randomized, controlled, open-label trial	4716	HCQ : 1561	3155	Overall, 418 (26.8%) patients allocated hydroxychloroquine and 788 (25.0%) patients allocated usual care died within 28 days (rate ratio 1.09; 95% confidence interval [CI] 0.96 to 1.23; P=0.18). [1] Consistent results were seen in all pre-specified subgroups of patients. [2] Patients allocated to hydroxychloroquine were less likely to be discharged from hospital alive within 28 days (60.3% vs. 62.8%; rate ratio 0.92; 95% CI 0.85-0.99) and those not on invasive mechanical ventilation at baseline were more likely to reach the composite endpoint of invasive mechanical ventilation or death (29.8% vs. 26.5%; risk ratio 1.12; 95% CI 1.01-1.25). [3] There was no excess of new major cardiac arrhythmia.	In patients hospitalized with COVID-19, hydroxychloroquine was not associated with reductions in 28-day mortality but was associated with an increased length of hospital stay and increased risk of progressing to invasive mechanical ventilation or death.	Yes	No	No	No	No	Yes	2020.7.15	High
NIH	1	RECOVERY Collaborative Group (2020)	randomized, controlled, open-label trial	4716	HCQ : 1561	3155	Overall, 418 (26.8%) patients allocated hydroxychloroquine and 788 (25.0%) patients allocated usual care died within 28 days (rate ratio 1.09; 95% confidence interval [CI] 0.96 to 1.23; P=0.18). [1] Consistent results were seen in all pre-specified subgroups of patients. [2] Patients allocated to hydroxychloroquine were less likely to be discharged from hospital alive within 28 days (60.3% vs. 62.8%; rate ratio 0.92; 95% CI 0.85-0.99) and those not on invasive mechanical ventilation at baseline were more likely to reach the composite endpoint of invasive mechanical ventilation or death (29.8% vs. 26.5%; risk ratio 1.12; 95% CI 1.01-1.25). [3] There was no excess of new major cardiac arrhythmia.	In patients hospitalized with COVID-19, hydroxychloroquine was not associated with reductions in 28-day mortality but was associated with an increased length of hospital stay and increased risk of progressing to invasive mechanical ventilation or death.	Yes	No	No	No	No	Yes	2020.7.15	High

	2	Cavalcanti AB (2020)	a multicenter, randomized, open-label, three-group, controlled trial	467	HCQ + AZ : 217, HCQ : 221	227	[1] As compared with standard care, the proportional odds of having a higher score on the seven-point ordinal scale at 15 days was not affected by either hydroxychloroquine alone (odds ratio, 1.21; 95% confidence interval [CI], 0.69 to 2.11; P=1.00) or hydroxychloroquine plus azithromycin (odds ratio, 0.99; 95% CI, 0.57 to 1.73; P=1.00). [2] Prolongation of the corrected QT interval and elevation of liver-enzyme levels were more frequent in patients receiving hydroxychloroquine, alone or with azithromycin, than in those who were not receiving either agent.	Among patients hospitalized with mild-to-moderate Covid-19, the use of hydroxychloroquine, alone or with azithromycin, did not improve clinical status at 15 days as compared with standard care.	Yes	No	No	No	No	Yes	2020.7.23	High
	3	Tang (2020)	Multi-center, open label, randomized, controlled	159	HCQ=75	75	[1] The negative conversion probability by 28 days in SOC plus HCQ group was 85.4% (95% confidence interval (CI) 73.8% to 93.8%), similar to that in the SOC group 81.3% (95%CI 71.2% to 89.6%). [2] Between-group difference was 4.1% (95%CI -10.3% to 18.5%).	The administration of HCQ did not result in a significantly higher negative conversion probability than SOC alone in patients mainly hospitalized with persistent mild to moderate COVID-19.	Yes	No	No	No	No	Yes	2020.5.7	High
	4	Borba MGS (2020)	double-blind, randomized, phase IIb clinical trial	81	low dose CQ = 40	high dose CQ = 41	[1] Viral RNA was detected in 31 of 40 (77.5%) and 31 of 41 (75.6%) patients in the low-dosage and high-dosage groups, respectively. [2] Lethality until day 13 was 39.0% in the high-dosage group (16 of 41) and 15.0% in the low-dosage group (6 of 40). [3] The high-dosage group presented more instance of QTc interval greater than 500 milliseconds (7 of 37 [18.9%]) compared with the low-dosage group (4 of 36 [11.1%]). [4] Respiratory secretion at day 4 was negative in only 6 of 27 patients (22.2%).	The preliminary findings of this study suggest that the higher CQ dosage should not be recommended for critically ill patients with COVID-19 because of its potential safety hazards, especially when taken concurrently with azithromycin and oseltamivir. These findings cannot be extrapolated to patients with nonsevere COVID-19.	Yes	Yes	Yes	Yes	No	Yes	2020.4	High
	5	Skipper CP (2020)	Multi center, randomized, double-blind, placebo-controlled trial	491	HCQ= 244	247	[1] Change in symptom severity over 14 days did not differ between the hydroxychloroquine and placebo groups (difference in symptom severity: relative, 12%; absolute, -0.27 point [95% CI, -0.61 to 0.07 point]; P = 0.117). [2] At 14 days, 24% (49 of 201) of participants receiving hydroxychloroquine had ongoing symptoms compared with 30% (59 of 194) receiving placebo (P = 0.21).	Hydroxychloroquine did not substantially reduce symptom severity in outpatients with early, mild COVID-19	Yes	Yes	Yes	Yes	No	Yes	2020.7.16	High
	6	Mitja O (2020)	multicenter, open label, randomized controlled trial	293	157	136	[1] No significant differences were found in the mean reduction of viral load at day 3 (-1.41 vs. -1.41 Log10 copies/mL in the control and intervention arm, respectively; difference 0.01 [95% CI -0.28;0.29]) or at day 7 (-3.37 vs. -3.44; d -0.07 [-0.44;0.29]). [2] This treatment regimen did not reduce risk of hospitalization (7.1%, control vs. 5.9%, intervention; RR 0.75 [0.32;1.77]) nor shortened the time to complete resolution of symptoms (12 days, control vs. 10 days, intervention; p = 0.38).	In patients with mild Covid-19, no benefit was observed with HCQ beyond the usual care.	Yes	No	No	No	No	Yes	2020.7.16	High
IDSA	1	RECOVERY Collaborative Group (2020)	randomized, controlled, open-label trial	4716	HCQ : 1561	3155	Overall, 418 (26.8%) patients allocated hydroxychloroquine and 788 (25.0%) patients allocated usual care died within 28 days (rate ratio 1.09; 95% confidence interval [CI] 0.96 to 1.23; P=0.18). [1] Consistent results were seen in all pre-specified subgroups of patients. [2] Patients allocated to hydroxychloroquine were less likely to be discharged from hospital alive within 28 days (60.3% vs. 62.8%; rate ratio 0.92; 95% CI 0.85-0.99) and those not on invasive mechanical ventilation at baseline were more likely to reach the composite endpoint of invasive mechanical ventilation or death (29.8% vs. 26.5%; risk ratio 1.12; 95% CI 1.01-1.25). [3] There was no excess of new major cardiac arrhythmia.	In patients hospitalized with COVID-19, hydroxychloroquine was not associated with reductions in 28-day mortality but was associated with an increased length of hospital stay and increased risk of progressing to invasive mechanical ventilation or death.	Yes	No	No	No	No	Yes	2020.7.15	moderate
	2	Cavalcanti AB (2020)	a multicenter, randomized, open-label, three-group, controlled trial	467	HCQ + AZ : 217, HCQ : 221	227	[1] As compared with standard care, the proportional odds of having a higher score on the seven-point ordinal scale at 15 days was not affected by either hydroxychloroquine alone (odds ratio, 1.21; 95% confidence interval [CI], 0.69 to 2.11; P=1.00) or hydroxychloroquine plus azithromycin (odds ratio, 0.99; 95% CI, 0.57 to 1.73; P=1.00). [2] Prolongation of the corrected QT interval and elevation of liver-enzyme levels were more frequent in patients receiving hydroxychloroquine, alone or with azithromycin, than in those who were not receiving either agent.	Among patients hospitalized with mild-to-moderate Covid-19, the use of hydroxychloroquine, alone or with azithromycin, did not improve clinical status at 15 days as compared with standard care.	Yes	No	No	No	No	Yes	2020.7.23	moderate

	3	Chen J (2020)	Randomized, controlled	60	HCQ= 30	30	[1] One patient in HCQ group developed to severe during the treatment. [2] On day 7, nucleic acid of throat swabs was negative in 13 (86.7%) cases in the HCQ group and 14 (93.3%) cases in the control group (P>0.05). [3] The median duration from hospitalization to virus nucleic acid negative conservation was 4 (1, 9) days in HCQ group, which is comparable to that in the control group [2 (1, 4) days, Z=1.27, P>0.05]. [4] The median time for body temperature normalization in HCQ group was 1 (0, 2) day after hospitalization, which was also comparable to that in the control group [1 (0, 3) day]. [5] Radiological progression was shown on CT images in 5 cases (33.3%) of the HCQ group and 7 cases (46.7%) of the control group, and all patients showed improvement in follow-up examinations. [6] Four cases (26.7%) of the HCQ group and 3 cases (20%) of the control group had transient diarrhea and abnormal liver function (P>0.05).	Larger sample size study are needed to investigate the effects of HCQ in the treatment of COVID-19.	Yes	No	No	No	Yes	No	2020.3.6	low
	4	Chen Z (2020)	Randomized, controlled, blind, single center	62	HCQ = 31	31	[1] No difference in the age and sex distribution between the control group and the HCQ group. [2] But for TTCR, the body temperature recovery time and the cough remission time were significantly shortened in the HCQ treatment group. [3] Besides, a larger proportion of patients with improved pneumonia in the HCQ treatment group (80.6%, 25 of 31) compared with the control group (54.8%, 17 of 31).	Among patients with COVID-19, the use of HCQ could significantly shorten TTCR and promote the absorption of pneumonia.	Yes	Yes	Yes	Yes	No	Yes	2020.4.10	low
	5	Tang (2020)	Multi-center, open label, randomized, controlled	159	HCQ=75	75	[1] The negative conversion probability by 28 days in SOC plus HCQ group was 85.4% (95% confidence interval (CI) 73.8% to 93.8%), similar to that in the SOC group 81.3% (95%CI 71.2% to 89.6%). [2] Between-group difference was 4.1% (95%CI -10.3% to 18.5%).	The administration of HCQ did not result in a significantly higher negative conversion probability than SOC alone in patients mainly hospitalized with persistent mild to moderate COVID-19.	Yes	No	No	No	No	Yes	2020.5.7	low
IDSA	**HCQ + AZM 병용 효능**														
	1	Cavalcanti AB (2020)	a multicenter, randomized, open-label, three-group, controlled trial	467	HCQ + AZ : 217, HCQ : 221	227	[1] As compared with standard care, the proportional odds of having a higher score on the seven-point ordinal scale at 15 days was not affected by either hydroxychloroquine alone (odds ratio, 1.21; 95% confidence interval [CI], 0.69 to 2.11; P=1.00) or hydroxychloroquine plus azithromycin (odds ratio, 0.99; 95% CI, 0.57 to 1.73; P=1.00). [2] Prolongation of the corrected QT interval and elevation of liver-enzyme levels were more frequent in patients receiving hydroxychloroquine, alone or with azithromycin, than in those who were not receiving either agent.	Among patients hospitalized with mild-to-moderate Covid-19, the use of hydroxychloroquine, alone or with azithromycin, did not improve clinical status at 15 days as compared with standard care.	Yes	No	No	No	No	Yes	2020.7.23	low
China	75	Tang (2020)	Multi-center, open label, randomized, controlled	159	HCQ=75	75	[1] The negative conversion probability by 28 days in SOC plus HCQ group was 85.4% (95% confidence interval (CI) 73.8% to 93.8%), similar to that in the SOC group 81.3% (95%CI 71.2% to 89.6%). [2] Between-group difference was 4.1% (95%CI -10.3% to 18.5%).	The administration of HCQ did not result in a significantly higher negative conversion probability than SOC alone in patients mainly hospitalized with persistent mild to moderate COVID-19.	Yes	No	No	No	No	Yes	2020.5.7	High
Bean		Self W (2020)	multicenter, blinded, placeb	479	HCQ : 242	237	[1] Among 479 patients who were randomized (median age, 57 years; 44.3% female; 37.2% Hispanic/Latinx; 23.4% Black; 20.1% in the intensive care unit; 46.8% receiving supplemental oxygen without positive pressure; 11.5% receiving noninvasive ventilation or nasal high-flow oxygen; and 6.7% receiving invasive mechanical ventilation or extracorporeal membrane oxygenation), 433 (90.4%) completed the primary outcome assessment at 14 days and the remainder had clinical status imputed. [2] The median duration of symptoms prior to randomization was 5 days (interquartile range [IQR], 3 to 7 days). [3] Clinical status on the ordinal outcome scale at 14 days did not significantly differ between the hydroxychloroquine and placebo groups (median [IQR] score, 6 [4-7] vs 6 [4-7]; aOR, 1.02 [95% CI, 0.73 to 1.42]). [4] None of the 12 secondary outcomes were significantly different between groups. [5] At 28 days after randomization, 25 of 241 patients (10.4%) in the hydroxychloroquine group and 25 of 236 (10.6%) in the placebo group had died (absolute difference, −0.2% [95% CI, −5.7% to 5.3%]; aOR, 1.07 [95% CI, 0.54 to 2.09]).	Among adults hospitalized with respiratory illness from COVID-19, treatment with hydroxychloroquine, compared with placebo, did not significantly improve clinical status at day 14. These findings do not support the use of hydroxychloroquine for treatment of COVID-19 among hospitalized adults.	Yes	Yes	Yes	Yes	No	Yes	2020.11.5	High

CQ2. 코로나 19 환자에게 hydroxychloroquine 혹은 hydroxychloroquine과 azithromycin 병합 투여가 도움이 되는가? [non-RCT]

선행가이드라인 표시	문헌번호	1저자 (출판연도)	연구유형	대상자 (N)	중재군(N)	비교/대조군 (N)	연구결과	결론	Quality Assessment (RoBANS)							
									대상자 비교가능성	대상자 선정	교란변수	노출측정	평가자의 눈가림	결과평가	불완전한 결과자료	선택적 결과보고
NIH	7	Rosenberg ES	Retrospective multicenter observational cohort study	1438	HCQ + AZM : 735, HCQ : 271, AZM : 211	221	[1] The probability of death for patients receiving hydroxychloroquine + azithromycin was 189/735 (25.7% [95% CI, 22.3%-28.9%]), hydroxychloroquine alone, 54/271 (19.9% [95% CI, 15.2%-24.7%]), azithromycin alone, 21/211 (10.0% [95% CI, 5.9%-14.0%]), and neither drug, 28/221 (12.7% [95% CI, 8.3%-17.1%]). [2] In adjusted Cox proportional hazards models, compared with patients receiving neither drug, there were no significant differences in mortality for patients receiving hydroxychloroquine + azithromycin (HR, 1.35 [95% CI, 0.76-2.40]), hydroxychloroquine alone (HR, 1.08 [95% CI, 0.63-1.85]), or azithromycin alone (HR, 0.56 [95% CI, 0.26-1.21]).	Among patients hospitalized in metropolitan New York with COVID-19, treatment with hydroxychloroquine, azithromycin, or both, compared with neither treatment, was not significantly associated with differences in in-hospital mortality.	낮음	낮음	낮음	낮음	높음	낮음	낮음	낮음
	8	Geleris J	Observational study	1376	HCQ : 811	565	[1] In the primary multivariable analysis with inverse probability weighting according to the propensity score, there was no significant association between hydroxychloroquine use and the composite primary end point (hazard ratio, 1.04; 95% CI, 0.82 to 1.32)	In this observational study involving patients with Covid-19 who had been admitted to the hospital, hydroxychloroquine administration was not associated with either a greatly lowered or an increased risk of the composite end point of intubation or death.	낮음	낮음	낮음	낮음	높음	낮음	낮음	낮음
	9	Mahevas M	Comparative observational study	173	HCQ : 84	89	[1] Eight additional patients received hydroxychloroquine more than 48 hours after admission. [2] In the weighted analyses, the survival rate without transfer to the intensive care unit at day 21 was 76% in the treatment group and 75% in the control group (weighted hazard ratio 0.9, 95% confidence interval 0.4 to 2.1). [3] Overall survival at day 21 was 89% in the treatment group and 91% in the control group (1.2, 0.4 to 3.3). [4] Survival without acute respiratory distress syndrome at day 21 was 69% in the treatment group compared with 74% in the control group (1.3, 0.7 to 2.6). [5] At day 21, 82% of patients in the treatment group had been weaned from oxygen compared with 76% in the control group (weighted risk ratio 1.1, 95% confidence interval 0.9 to 1.3)	The results of this study do not support its use in patients admitted to hospital with covid-19 who require oxygen.	낮음	낮음	낮음	낮음	높음	낮음	낮음	낮음
	10	Arshad S	comparative retrospective cohort study	2541	HCQ : 1202, AZM : 147, HCQ + AZM : 783	409	[1] Overall in-hospital mortality was 18.1% (95% CI:16.6%–19.7%); by treatment: hydroxychloroquine + azithromycin, 157/783 (20.1% [95% CI: 17.3%–23.0%]), hydroxychloroquine alone, 162/1202 (13.5% [95% CI: 11.6%–15.5%]), azithromycin alone, 33/147 (22.4% [95% CI: 16.0%–30.1%]), and neither drug, 108/409 (26.4% [95% CI: 22.2%–31.0%]). [2] Primary cause of mortality was respiratory failure (88%); no patient had documented torsades de pointes. From Cox regression modeling, predictors of mortality were age>65 years (HR:2.6 [95% CI:1.9–3.3]), white race (HR:1.7 [95% CI:1.4–2.1]), CKD (HR:1.7 [95%CI:1.4–2.1]), reduced O2 saturation level on admission (HR:1.5 [95%CI:1.1–2.1]), and ventilator use during admission (HR: 2.2 [95%CI:1.4–3.3]). Hydroxychloroquine provided a 66% hazard ratio reduction, and hydroxychloroquine + azithromycin 71% compared to neither treatment (p<0.001).	: In this multi-hospital assessment, when controlling for COVID-19 risk factors, treatment with hydroxychloroquine alone and in combination with azithromycin was associated with reduction in COVID-19 associated mortality.	낮음	낮음	높음	낮음	높음	낮음	낮음	낮음
	13	Gautret P (2020)	uncontrolled, non-comparative, observational study	80	80		[1] All patients improved clinically except one 86 year-old patient who died, and one 74 year-old patient still in intensive care. [2] A rapid fall of nasopharyngeal viral load was noted, with 83% negative at Day7, and 93% at Day8. [3] Virus cultures from patient respiratory samples were negative in 97.5% of patients at Day5. [4] Consequently patients were able to be rapidly discharged from IDU with a mean length of stay of five days.	We believe there is urgency to evaluate the effectiveness of this potentially-life saving therapeutic strategy at a larger scale, both to treat and cure patients at an early stage before irreversible severe respiratory complications take hold and to decrease duration of carriage and avoid the spread of the disease.	높음	높음	높음	높음	높음	높음	높음	높음

	14	Gautret P (2020)	open-label non-randomized clinical trial	36	HCQ : 20	16	[1] Six patients were asymptomatic, 22 had upper respiratory tract infection symptoms and eight had lower respiratory tract infection symptoms. [2] Twenty cases were treated in this study and showed a significant reduction of the viral carriage at D6-post inclusion compared to controls, and much lower average carrying duration than reported in the litterature for untreated patients. [3] Azithromycin added to hydroxychloroquine was significantly more efficient for virus elimination.	Despite its small sample size, our survey shows that hydroxychloroquine treatment is significantly associated with viral load reduction/disappearance in COVID-19 patients and its effect is reinforced by azithromycin.	높음	높음	높음	높음	높음	높음	높음	높음
	15	Huang M (2020)	open-label, randomized clinical trial	22	HCQ : 10	Kaletra : 12	[1] Comparing to the Lopinavir/Ritonavir group, the percentages of patients who became SARS-CoV-2 negative in the Chloroquine group were slightly higher at Day 7, Day 10, and Day 14. [2] These results suggest that Chloroquine has slight advantage over Lopinavir/Ritonavir based on RNA tests. [3]By Day 14, the incidence rate of lung improvement based on CT imaging from the Chloroquine group was more than doubled to that of the Lopinavir/Ritonavir group (rate ratio 2.21, 95% CI 0.81–6.62). These results suggest that patients treated with Chloroquine appear to recover better and regain their pulmonary function quicker than those treated with Lopinavir/Ritonavir. [4] Chloroquine group were discharged compared to 6 patients (50%) from the Lopinavir/Ritonavir group. [5] Furthermore, Chloroquine also appeared to promote quicker recovery compared to Lopinavir/Ritonavir recommended by health authorities in China.	In sum, our preliminary results suggest that Chloroquine could be an effective and inexpensive option among many proposed therapies, e.g. Lopinavir/Ritonavir. Considering the severe epidemic and short supply of medical resource, our study was limited by small sample size.	높음	높음	높음	높음	높음	높음	높음	높음
	16	Magagnoli J (2020)	a retrospective analysis	368	HCQ : 97, HCQ+AZM : 113	158	[1] Rates of ventilation in the HC, HC+AZ, and no HC groups were 13.3%, 6.9%, 14.1%, respectively. [2] Compared to the no HC group, the risk of death from any cause was higher in the HC group (adjusted hazard ratio, 2.61; 95% CI, 1.10 to 6.17; P=0.03) but not in the HC+AZ group (adjusted hazard ratio, 1.14; 95% CI, 0.56 to 2.32; P=0.72). [3] The risk of ventilation was similar in the HC group (adjusted hazard ratio, 1.43; 95% CI, 0.53 to 3.79; P=0.48) and in the HC+AZ group (adjusted hazard ratio, 0.43; 95% CI, 0.16 to 1.12; P=0.09), compared to the no HC group.	[1] In this study, we found no evidence that use of hydroxychloroquine, either with or without azithromycin, reduced the risk of mechanical ventilation in patients hospitalized with Covid-19. [2] An association of increased overall mortality was identified in patients treated with hydroxychloroquine alone.	낮음	낮음	낮음	낮음	높음	낮음	낮음	낮음
	17	Molina JM	prospecitve observational study	11	HCQ + AZM : 11		[1] At the time of treatment initiation, 10/11 had fever and received nasal oxygen therapy. Within 5 days, one patient died, two were transferred to the ICU. [2] In one patient, hydroxychloroquine and azithromycin were discontinued after 4 days because of a prolongation of the QT interval from 405 ms before treatment to 460 and 470 ms under the combination. Mean through blood concentration of hydroxychloroquine was 678 ng/mL (range: 381–891) at days 3–7 after treatment initiation. [4] Repeated nasopharyngeal swabs in 10 patients (not done in the patient who died) using a qualitative PCR assay (nucleic acid extraction using Nuclisens Easy Mag®, Biomerieux and amplification with RealStar SARS CoV-2®, Altona), were still positive for SARS-CoV2 RNA in 8/10 patients (80%, 95% confidence interval: 49–94) at days 5 to 6 after treatment initiation. [5] These virologic results stand in contrast with those reported by Gautret et al. and cast doubts about the strong antiviral efficacy of this combination. [6]Furthermore, in their report Gautret et al. also reported one death and three transfers to the ICU among the 26 patients who received hydroxychloroquine, also underlining the poor clinical outcome with this combination.	In summary, despite a reported antiviral activity of chloroquine against COVID-19 in vitro, we found no evidence of a strong antiviral activity or clinical benefit of the combination of hydroxychloroquine and azithromycin for the treatment of our hospitalised patients with severe COVID-19.	높음	높음	높음	높음	높음	높음	높음	높음

	18	Satlin MJ (2020)	retrospective multicenter observational cohort study	153	HCQ : 153		[1] None of the 153 hospitalized patients with COVID-19 who received HCQ developed a sustained ventricular tachyarrhythmia. Incident blood count and liver test abnormalities occurred in <15% of patients and incident vomiting or diarrhea was rare. [2] Eighty-nine percent of patients completed their HCQ course and three patients discontinued therapy because of QT prolongation. Fifty-two percent of patients had improved hypoxia scores 10 days after starting HCQ. [3] Thirty-one percent of patients who were receiving mechanical ventilation at the time of HCQ initiation died during their hospitalization, compared to 18% of patients who were receiving supplemental oxygen but not requiring mechanical ventilation, and 8% of patients who were not requiring supplemental oxygen. [4] Co-administration of azithromycin was not associated with improved outcomes.	HCQ appears to be reasonably safe and tolerable in most hospitalized patients with COVID-19. However, nearly one-half of patients did not improve with this treatment, highlighting the need to evaluate HCQ and alternate therapies in randomized trials.	높음	높음	높음	높음	높음	높음	높음	높음
	19	Mikami T (2020)	Retrospective multicenter cohort study	6493	HCQ : 2863, AZM : 2785		[1] A total of 858 of 6493 (13.2%) patients in our total cohort died: 52/2785 (1.9%) ambulatory patients and 806/3708 (21.7%) hospitalized patients. [2] Cox proportional hazard regression modeling showed an increased risk of in-hospital mortality associated with age older than 50 years (hazard ratio [HR] 2.34, CI 1.47–3.71), systolic blood pressure less than 90 mmHg (HR 1.38, CI 1.06–1.80), a respiratory rate greater than 24 per min (HR 1.43, CI 1.13–1.83), peripheral oxygen saturation less than 92% (HR 2.12, CI 1.56–2.88), estimated glomerular filtration rate less than 60 mL/min/1.73m2 (HR 1.80, CI 1.60–2.02), IL-6 greater than 100 pg/mL (HR 1.50, CI 1.12–2.03), D-dimer greater than 2 mcg/mL (HR 1.19, CI 1.02–1.39), and troponin greater than 0.03 ng/mL (HR 1.40, CI 1.23–1.62). [3] Decreased risk of in-hospital mortality was associated with female sex (HR 0.84, CI 0.77–0.90), African American race (HR 0.78 CI 0.65–0.95), and hydroxychloroquine use (HR 0.53, CI 0.41–0.67).	Among patients with COVID-19, older age, male sex, hypotension, tachypnea, hypoxia, impaired renal function, elevated D-dimer, and elevated troponin were associated with increased in-hospital mortality and hydroxychloroquine use was associated with decreased in-hospital mortality.	높음	높음	높음	높음	높음	높음	높음	높음
	20	Catteau L (2020)	retrospective cohort study	8075	HCQ : 4542	3533	[1] Of 8075 patients with complete discharge data on 24 May 2020 and diagnosed before 1 May 2020, 4542 received HCQ in monotherapy and 3533 were in the no-HCQ group. Death was reported in 804/4542 (17.7%) and 957/3533 (27.1%), respectively. In the multivariable analysis, mortality was lower in the HCQ group compared with the no-HCQ group [adjusted hazard ratio (aHR) = 0.684, 95% confidence interval (CI) 0.617–0.758]. Compared with the no-HCQ group, mortality in the HCQ group was reduced both in patients diagnosed ≤5 days (n = 3975) and >5 days (n = 3487) after symptom onset [aHR = 0.701 (95% CI 0.617–0.796) and aHR = 0.647 (95% CI 0.525–0.797), respectively].	Compared with supportive care only, low-dose HCQ monotherapy was independently associated with lower mortality in hospitalised patients with COVID-19 diagnosed and treated early or later after symptom onset.	많음	많음	많음	많음	높음	많음	많음	많음
	21	Covid R (2020)	Retrospective multicenter cohort study	3451	HCQ : 2634	817	[1] Out of 3,451 COVID-19 patients, 76.3% received HCQ. Death rates (per 1,000 person-days) for patients receiving or not HCQ were 8.9 and 15.7, respectively. [2] After adjustment for propensity scores, we found 30% lower risk of death in patients receiving HCQ (HR=0.70; 95%CI: 0.59 to 0.84; E-value=1.67). [3] Secondary analyses yielded similar results. [4] The inverse association of HCQ with inpatient mortality was particularly evident in patients having elevated C-reactive protein at entry.	[1] HCQ use was associated with a 30% lower risk of death in COVID-19 hospitalized patients. [2] Within the limits of an observational study and awaiting results from randomized controlled trials, these data do not discourage the use of HCQ in inpatients with COVID-19.	많음	많음	많음	많음	높음	많음	많음	많음
	22	Furtado RHM (2020)	multi center, open-label, randomised clinical trial	447	HCQ + AZM : 237	HCQ : 210	[1] 447 patients were enrolled from March 28 to May 19, 2020. COVID-19 was confirmed in 397 patients who constituted the mITT population, of whom 214 were assigned to the azithromycin group and 183 to the control group. [2] In the mITT population, the primary endpoint was not significantly different between the azithromycin and control groups (OR 1·36 [95% CI 0·94-1·97], p=0·11). [3] Rates of adverse events, including clinically relevant ventricular arrhythmias, resuscitated cardiac arrest, acute kidney failure, and corrected QT interval prolongation, were not significantly different between groups.	[1] In patients with severe COVID-19, adding azithromycin to standard of care treatment (which included hydroxychloroquine) did not improve clinical outcomes. [2] Our findings do not support the routine use of azithromycin in combination with hydroxychloroquine in patients with severe COVID-19.	많음	많음	많음	많음	높음	많음	많음	많음

IDSA	6	Rosenberg ES	Retrospective multicenter observational cohort study	1438	HCQ + AZM : 735, HCQ : 271, AZM : 211	221	[1] The probability of death for patients receiving hydroxychloroquine + azithromycin was 189/735 (25.7% [95% CI, 22.3%-28.9%]), hydroxychloroquine alone, 54/271 (19.9% [95% CI, 15.2%-24.7%]), azithromycin alone, 21/211 (10.0% [95% CI, 5.9%-14.0%]), and neither drug, 28/221 (12.7% [95% CI, 8.3%-17.1%]). [2] In adjusted Cox proportional hazards models, compared with patients receiving neither drug, there were no significant differences in mortality for patients receiving hydroxychloroquine + azithromycin (HR, 1.35 [95% CI, 0.76-2.40]), hydroxychloroquine alone (HR, 1.08 [95% CI, 0.63-1.85]), or azithromycin alone (HR, 0.56 [95% CI, 0.26-1.21]).	Among patients hospitalized in metropolitan New York with COVID-19, treatment with hydroxychloroquine, azithromycin, or both, compared with neither treatment, was not significantly associated with differences in in-hospital mortality.	음성	음성	음성	음성	높음	음성	음성	음성
	7	Mahevas M	Comparative observational study	173	HCQ : 84	89	[1] Eight additional patients received hydroxychloroquine more than 48 hours after admission. [2] In the weighted analyses, the survival rate without transfer to the intensive care unit at day 21 was 76% in the treatment group and 75% in the control group (weighted hazard ratio 0.9, 95% confidence interval 0.4 to 2.1). [3] Overall survival at day 21 was 89% in the treatment group and 91% in the control group (1.2, 0.4 to 3.3). [4] Survival without acute respiratory distress syndrome at day 21 was 69% in the treatment group compared with 74% in the control group (1.3, 0.7 to 2.6). [5] At day 21, 82% of patients in the treatment group had been weaned from oxygen compared with 76% in the control group (weighted risk ratio 1.1, 95% confidence interval 0.9 to 1.3)	The results of this study do not support its use in patients admitted to hospital with covid-19 who require oxygen.	높음	높음	높음	높음	높음	높음	높음	높음
IDSA	**HCQ + AZM 병용 효능**																
	2	Rosenberg ES	Retrospective multicenter observational cohort study	1438	HCQ + AZM : 735, HCQ : 271, AZM : 211	221	[1] The probability of death for patients receiving hydroxychloroquine + azithromycin was 189/735 (25.7% [95% CI, 22.3%-28.9%]), hydroxychloroquine alone, 54/271 (19.9% [95% CI, 15.2%-24.7%]), azithromycin alone, 21/211 (10.0% [95% CI, 5.9%-14.0%]), and neither drug, 28/221 (12.7% [95% CI, 8.3%-17.1%]). [2] In adjusted Cox proportional hazards models, compared with patients receiving neither drug, there were no significant differences in mortality for patients receiving hydroxychloroquine + azithromycin (HR, 1.35 [95% CI, 0.76-2.40]), hydroxychloroquine alone (HR, 1.08 [95% CI, 0.63-1.85]), or azithromycin alone (HR, 0.56 [95% CI, 0.26-1.21]).	Among patients hospitalized in metropolitan New York with COVID-19, treatment with hydroxychloroquine, azithromycin, or both, compared with neither treatment, was not significantly associated with differences in in-hospital mortality.	음성	음성	음성	음성	높음	음성	음성	음성
	3	Maganoli J (2020)	Retrospective study	807	HCQ : 198, HCQ +	395	[1] Compared to the no HC group, after propensity score adjustment for clinical characteristics, the risk of death from any cause was higher in the HC group (adjusted hazard ratio [aHR], 1.83; 95% confidence interval [CI], 1.16–2.89; p = 0.009), but not in the HC+AZ group (aHR, 1.31; 95% CI, 0.80–2.15; p = 0.28). [2] Both the propensity-score-adjusted risks of mechanical ventilation and death after mechanical ventilation were not significantly different in the HC group (aHR, 1.19; 95% CI, 0.78–1.82; p = 0.42 and aHR, 2.11; 95% CI, 0.96–4.62; p = 0.06, respectively) or in the HC+AZ group (aHR, 1.09; 95% CI, 0.72–1.66; p = 0.69 and aHR, 1.25; 95% CI, 0.59–2.68; p = 0.56, respectively) compared to the no HC group.	Among patients hospitalized with COVID-19, this retrospective study did not identify any significant reduction in mortality or in the need for mechanical ventilation with hydroxychloroquine treatment with or without azithromycin.	음성	음성	음성	음성	높음	음성	음성	음성

	4	Ip A (2020)	Retrospective observational cohort study	2512	HCQ : 1914	598	[1] Among 2512 hospitalized patients with COVID-19 there have been 547 deaths (22%), 1539 (61%) discharges and 426 (17%) remain hospitalized. 1914 (76%) received at least one dose of hydroxychloroquine and 1473 (59%) received hydroxychloroquine with azithromycin. [2] After adjusting for imbalances via propensity modeling, compared to receiving neither drug, there were no significant differences in associated mortality for patients receiving any hydroxychloroquine during the hospitalization (HR, 0.99 [95% CI, 0.80-1.22]), hydroxychloroquine alone (HR, 1.02 [95% CI, 0.83-1.27]), or hydroxychloroquine with azithromycin (HR, 0.98 [95% CI, 0.75-1.28]). [3] The 30-day unadjusted mortality for patients receiving hydroxychloroquine alone, azithromycin alone, the combination or neither drug was 25%, 20%, 18%, and 20%, respectively. [4] Among 547 evaluable ICU patients, including 134 receiving tocilizumab in the ICU, an exploratory analysis found a trend towards an improved survival association with tocilizumab treatment (adjusted HR, 0.76 [95% CI, 0.57-1.00]), with 30 day unadjusted mortality with and without tocilizumab of 46% versus 56%.	This observational cohort study suggests hydroxychloroquine, either alone or in combination with azithromycin, was not associated with a survival benefit among hospitalized COVID-19 patients. Tocilizumab demonstrated a trend association towards reduced mortality among ICU patients. Our findings are limited to hospitalized patients and must be interpreted with caution while awaiting results of randomized trials.	없음	없음	없음	없음	없음	없음	없음	없음
	5	Gautret P (2020)	open-label non-randomized clinical trial	36	HCQ : 20	16	[1] Six patients were asymptomatic, 22 had upper respiratory tract infection symptoms and eight had lower respiratory tract infection symptoms. [2] Twenty cases were treated in this study and showed a significant reduction of the viral carriage at D6-post inclusion compared to controls, and much lower average carrying duration than reported in the litterature for untreated patients. [3] Azithromycin added to hydroxychloroquine was significantly more efficient for virus elimination.	Despite its small sample size, our survey shows that hydroxychloroquine treatment is significantly associated with viral load reduction/disappearance in COVID-19 patients and its effect is reinforced by azithromycin.	있음	있음	있음	있음	있음	있음	있음	있음
	6	Gautret P (2020)	uncontrolled, non-comparative, observational study	80	80		[1] All patients improved clinically except one 86 year-old patient who died, and one 74 year-old patient still in intensive care. [2] A rapid fall of nasopharyngeal viral load was noted, with 83% negative at Day7, and 93% at Day8. [3] Virus cultures from patient respiratory samples were negative in 97.5% of patients at Day5. [4] Consequently patients were able to be rapidly discharged from IDU with a mean length of stay of five days.	We believe there is urgency to evaluate the effectiveness of this potentially-life saving therapeutic strategy at a larger scale, both to treat and cure patients at an early stage before irreversible severe respiratory complications take hold and to decrease duration of carriage and avoid the spread of the disease.	있음	있음	있음	있음	있음	있음	있음	있음
	7	Molina JM	prospecitve observational study	11	HCQ + AZM : 11		[1] At the time of treatment initiation, 10/11 had fever and received nasal oxygen therapy. Within 5 days, one patient died, two were transferred to the ICU. [2] In one patient, hydroxychloroquine and azithromycin were discontinued after 4 days because of a prolongation of the QT interval from 405 ms before treatment to 460 and 470 ms under the combination. Mean through blood concentration of hydroxychloroquine was 678 ng/mL (range: 381–891) at days 3–7 after treatment initiation. [4] Repeated nasopharyngeal swabs in 10 patients (not done in the patient who died) using a qualitative PCR assay (nucleic acid extraction using Nuclisens Easy Mag®, Biomerieux and amplification with RealStar SARS CoV-2®, Altona), were still positive for SARS-CoV2 RNA in 8/10 patients (80%, 95% confidence interval: 49–94) at days 5 to 6 after treatment initiation. [5] These virologic results stand in contrast with those reported by Gautret et al. and cast doubts about the strong antiviral efficacy of this combination. [6]Furthermore, in their report Gautret et al. also reported one death and three transfers to the ICU among the 26 patients who received hydroxychloroquine, also underlining the poor clinical outcome with this combination.	In summary, despite a reported antiviral activity of chloroquine against COVID-19 in vitro, we found no evidence of a strong antiviral activity or clinical benefit of the combination of hydroxychloroquine and azithromycin for the treatment of our hospitalised patients with severe COVID-19.	있음	있음	있음	있음	있음	있음	있음	있음
	8	Chorin E (2020)	retrospective observational study	84	HCQ + AZ :84		[1] In our work, we found that in patients with COVID-19 who were treated with HY/AZ, the QTc was significantly prolonged. [2] This discrepancy suggests that QT prolongation may be influenced by patient attributes such as the presence of co-morbidities and the severity of the disease9. [3] Of note, recent guidance suggested ECG screening with QTc assessment for patients with COVID-19 who are candidates for novel therapies, including HY/AZ10. In our cohort, five of nine patients with severe QTc prolongation had a normal QTc at baseline.	We therefore suggest that the QTc should be followed repeatedly in patients with COVID-19 who are treated with HY/AZ, particularly in those with co-morbidities and in those who are treated with other QT-prolonging medications.	있음	있음	있음	있음	있음	있음	있음	있음

China	73	Elavarasi A, (2020)	systemic review	10659	CQ/HCQ: 5713	4966	[1] We reviewed 12 observational and 3 randomized trials which included 10659 patients of whom 5713 received CQ/HCQ and 4966 received only standard of care. [2] The efficacy of CQ/HCQ for COVID-19 was inconsistent across the studies. [3] Meta-analysis of included studies revealed no significant reduction in mortality with HCQ use [RR 0.98 95% CI 0.66-1.46] , time to fever resolution [mean difference -0.54 days (-1.19-011)] or clinical deterioration/development of ARDS with HCQ [RR 0.90 95% CI 0.47-1.71]. [4] There was a higher risk of ECG abnormalities/arrhythmia with HCQ/CQ [RR 1.46 95% CI 1.04 to 2.06]. [5] The quality of evidence was graded as very low for these outcomes.	The available evidence suggests that CQ or HCQ does not improve clinical outcomes in COVID-19. Well-designed randomized trials are required for assessing the efficacy and safety of HCQ and CQ for COVID-19.	높음	높음	높음	높음	높음	높음	높음	높음
	74	Hernandez AV (2020)	systemic review				Several studies found that patients receiving hydroxychloroquine developed a QTc interval of 500 ms or greater, but the proportion of patients with this finding varied among the studies. Two studies assessed the efficacy of chloroquine; 1 trial, which compared higher-dose (600 mg twice daily for 10 days) with lower-dose (450 mg twice daily on day 1 and once daily for 4 days) therapy, was stopped owing to concern that the higher dose therapy increased lethality and QTc interval prolongation. An observational study that compared adults with COVID-19 receiving chloroquine phosphate, 500 mg once or twice daily, with patients not receiving chloroquine found minor fever resolution and virologic clearance benefits with chloroquine.	Evidence on the benefits and harms of using hydroxychloroquine or chloroquine to treat COVID-19 is very weak and conflicting.	높음	높음	높음	높음	높음	높음	높음	높음
	77	Magagnoli J (2020)	a retrospective analysis	368	HCQ : 97, HCQ+AZM : 113	158	[1] Rates of ventilation in the HC, HC+AZ, and no HC groups were 13.3%, 6.9%, 14.1%, respectively. [2] Compared to the no HC group, the risk of death from any cause was higher in the HC group (adjusted hazard ratio, 2.61; 95% CI, 1.10 to 6.17; P=0.03) but not in the HC+AZ group (adjusted hazard ratio, 1.14; 95% CI, 0.56 to 2.32; P=0.72). [3] The risk of ventilation was similar in the HC group (adjusted hazard ratio, 1.43; 95% CI, 0.53 to 3.79; P=0.48) and in the HC+AZ group (adjusted hazard ratio, 0.43; 95% CI, 0.16 to 1.12; P=0.09), compared to the no HC group.	[1] In this study, we found no evidence that use of hydroxychloroquine, either with or without azithromycin, reduced the risk of mechanical ventilation in patients hospitalized with Covid-19. [2] An association of increased overall mortality was identified in patients treated with hydroxychloroquine alone.	높음	높음	높음	높음	높음	높음	높음	높음
NECA 검색 ᄎ	100	Paccoud O (2020)	observational retrospective study	84	HCQ : 38	46	[1] Data from 89 patients with laboratory-confirmed Covid-19 were analyzed, 84 of whom were considered in the primary analysis; 38 patients treated with hydroxychloroquine and 46 patients treated with SOCalone. [2] At admission, the mean age of patients was 66 years, the median Charlson comorbidity index was 3, and the median NEWS2 severity score was 3. [3] After propensity score weighting, treatment with hydroxycholoroquine was not associated with a significantly reduced risk of unfavorable outcome (HR 0.90 [0.38; 2.1], p = 0.81). [4] Overall survival was not significantly different between the two groups (HR 0.89 [0.23; 3.47], p = 1)	[1] In hospitalized adults with Covid-19, no significant reduction of the risk of unfavorable outcomes was observed with hydroxychloroquine in comparison to standard of care. [2] Unmeasured confounders may however have persisted despite careful propensity-weighted analysis and the study might be underpowered. [3] Ongoing controlled trials in patients with varying degrees of initial severity on a larger scale will help determine whether there is a place for hydroxychloroquine in the treatment of Covid-19.	높음	높음	높음	높음	높음	높음	높음	높음
	221	Kim J (2020)	retrospective cohort study	65	HCQ : 34	LPV/r : 31	[1] Of 65 patients (mean age, 64.3 years; 25 men [38.5%]), 31 were treated with lopinavir-ritonavir and 34 were treated with hydroxychloroquine. [2] The median duration of symptoms before treatment was 7 days and 26 patients (40%) required oxygen support at baseline. [3] Patients treated with lopinavir-ritonavir had a significantly shorter time to negative conversion of viral RNA than those treated with hydroxychloroquine (median, 21 days vs. 28 days). [4] Treatment with lopinavir-ritonavir (adjusted hazard ratio [aHR], 2.28; 95% confidence interval [CI], 1.24 to 4.21) and younger age (aHR, 2.64; 95% CI 1.43 to 4.87) was associated with negative conversion of viral RNA. [5] There was no significant difference in time to clinical improvement between lopinavir-ritonavir- and hydroxychloroquine-treated patients (median, 18 days vs. 21 days). [6] Lymphopenia and hyperbilirubinemia were more frequent in lopinavir-ritonavir-treated patients compared with hydroxychloroquine-treated patients.	Lopinavir-ritonavir was associated with more rapid viral clearance than hydroxychloroquine in mild to moderate COVID-19, despite comparable clinical responses. These findings should be confirmed in randomized, controlled trials.	높음	높음	높음	높음	높음	높음	높음	높음

	298	The COVID-19 RISK and Treatments (CORIST) Collaboration (2020)	retrospecitve observational study	3451	HCQ : 817	2634	[1] Out of 3,451 COVID-19 patients, 76.3% received HCQ. Death rates (per 1,000 person-days) for patients receiving or not HCQ were 8.9 and 15.7, respectively. After adjustment for propensity scores, we found 30% lower risk of death in patients receiving HCQ (HR=0.70; 95%CI: 0.59 to 0.84; E-value=1.67). [2] Secondary analyses yielded similar results. The inverse association of HCQ with inpatient mortality was particularly evident in patients having elevated C-reactive protein at entry.	HCQ use was associated with a 30% lower risk of death in COVID-19 hospitalized patients. Within the limits of an observational study and awaiting results from randomized controlled trials, these data do not discourage the use of HCQ in inpatients with COVID-19.	높음	높음	높음	높음	높음	높음	높음	높음
	305	Szente Fonseca (2020)	retrospective observational study	717	HCQ : 175, HCQ + PD : 159	PD : 139, Neither HCQ nor PD : 159, None medi : 122	[1] Use of hydroxychloroquine (HCQ), prednisone or both significantly reduced hospitalization risk by 50–60%. Ivermectin, azithromycin and oseltamivir did not substantially reduce risk further. Hospitalization risk was doubled for people with type-2 diabetes or obesity, increased by two-thirds for people with heart disease, and by 75% for each decade of age over age 40. Similar magnitudes of reduced risk with HCQ and prednisone use were seen for mortality risk, though were not significant because of only 11 deaths among the 717 patients. [2] No cardiac arrhythmias requiring medication termination were observed for any of the medications.	[1] This work adds to the growing literature of studies that have found substantial benefit for use of HCQ combined with other agents in the early outpatient treatment of COVID-19, and adds the possibility of steroid use to enhance treatment efficacy.	높음	높음	높음	높음	높음	높음	높음	높음
	449	Annie F (2020)	Retrospective propensity matched cohort study	3012	HCQ : 367, HCQ + AZM : 199	non HCQ : 367, non HCQ+ AZM : 199	[1] Among patients with a diagnosis of COVID-19 in our propensity-matched cohort, the mean ages ± SD were 62.3 ± 15.9 years (53.7% male) and 61.9 ± 16.0 years (53.0% male) in the HCQ and no-HCQ groups, respectively. [2] There was no difference in overall 30-day mortality between the HCQ and no-HCQ groups (HCQ 13.1%, n=367; no HCQ 13.6%, n=367; odds ratio 0.95, 95% confidence interval 0.62–1.46) after propensity matching. [3] Although statistically insignificant, the HCQ-azithromycin (AZ) group had an overall mortality rate of 14.6% (n=199) compared with propensity-matched no-HCQ–AZ cohort's rate of 12.1% (n=199, OR 1.24, 95% CI 0.70–2.22). [4] Importantly, however, there was no trend in this cohort's overall mortality/arrhythmogenesis outcome (HCQ-AZ 17.1%, no HCQ–no AZ 17.1%; OR 1.0, 95% CI 0.6–1.7).	We report from a large retrospective multinational database analysis of COVID-19 outcomes with HCQ and overall mortality in hospitalized patients. There was no statistically significant increase in mortality and mortality-arrhythmia with HCQ or HCQ-AZ.	낮음	낮음	낮음	높음	높음	낮음	낮음	낮음
	453	Huang HD (2020)	retrospective cohort study	346	HCQ + AZM : 173	173	[1] Propensity-matched groups were composed of 173 patients given HCQ-AZM and 173 matched patients who did not receive treatment. [2] There was no significant difference in in-hospital mortality (odds ratio [OR] 1.52; 95% confidence interval [CI] 0.80–2.89; p = 0.2), PEA arrest (OR 1.68, CI 0.68–4.15; p = 0.27), or incidence of non-lethal arrhythmias (10.4% vs. 6.8%; p = 0.28). [3] Length of hospital stay (10.5 ± 7.4 vs. 5.8 ± 6.1; p < 0.001), peak CRP levels (252 ± 136 vs. 166 ± 124; p < 0.0001), and degree of QTc interval prolongation was higher for the HCQ-AZM group (28 ± 32 vs. 9 ± 32; p < 0.0001), but there was no significant difference in incidence of sustained ventricular arrhythmias (2.8% vs. 1.7%; p = 0.52). [4] HCQ-AZM was stopped in 10 patients because of QT interval prolongation and 1 patient because of drug-related polymorphic ventricular tachycardia.	[1] In this propensity-matched study, there was no difference in in-hospital mortality, life-threatening arrhythmias, or incidence of PEA arrest between the HCQ-AZM and untreated control groups. [2] QTc intervals were longer in patients receiving HCQ-AZM, but only one patient developed drug-related ventricular tachycardia.	낮음	낮음	낮음	낮음	불확실	낮음	낮음	낮음
	456	Lammers A (2020)	observational cohort study	1064	HCQ: 189, CQ : 377	498	[1] The analysis contained 1064 patients from 14 hospitals: 566 patients received treatment with either HCQ (n = 189) or CQ (n = 377), and 498 patients received no treatment. [2] In a multivariate propensity matched weighted competing regression analysis, there was no significant effect of (H)CQ on mortality on the COVID-ward. [3] HCQ however was associated with a significant decreased risk of transfer to the ICU (Hazard ratio (HR) = 0.47, 95%CI = 0.27-0.82, p = 0.008), when compared to controls. [4] This effect was not found in the CQ group (HR = 0.80; 95%CI = 0.55-1.15, p = 0.207), and remained significant after competing risk analysis.	[1] The results of this observational study demonstrate a lack of effect of (H)CQ on non-ICU mortality. [2] However, we show that the use of HCQ - but not CQ - is associated with 53% decreased risk of transfer of COVID-19 patients from the regular ward to the ICU. [3] Recent prospective studies have reported on 28 days all-cause mortality only, therefore additional prospective data on the early effect of HCQ in preventing transfer to the ICU is still needed.	높음	높음	높음	높음	높음	높음	높음	높음

	661	Bernardini A (2020)	retrospective study	112	HCQ mono : 40, HCA + AZM : 53	19	[1] A prolonged QTc interval was found in 61% of patients treated with HCQ alone or in combination with AZT, but only 4 (4%) patients showed a QTc > 500 ms. [2] HCQ/AZT combination determined a greater increase of QTc duration compared to the other two strategies (Group 3 452 ± 26.4 vs Group 2 436.3 ± 28.4 vs Group 1 424.4 ± 24.3 ms, respectively; p < 0.001). [3] Multivariate analysis demonstrated that HCQ/AZT combination (OR 9.02, p = 0.001) and older age (OR 1.04, p = 0.031) were independent predictors of QTc prolongation. [4] The risk increased with age (incremental utility analysis p = 0.02). [5] Twenty patients (18%) died, and no cardiac arrest neither arrhythmic fatalities were documented.	[1] The HCQ/AZT combination therapy causes a significantly increase of QT interval compared to HCQ alone. [2] Older patients under such regimen are at higher risk of experiencing QT prolongation. [3] The use of such drugs may be considered as safe relating to arrhythmic risk in the treatment of COVID-19 patients as no arrhythmic fatalities occurred.	높음	높음	높음	높음	높음	높음	높음	높음
	671	Karoly M (2020)	a retrospective single center observational cohort study	67	HCQ : 20	LPV/r : 47	[1] Of 156 patients (41% female) with a median age of 72 years (IQR 55.25-81) admitted to our department, 67 patients fulfilled the inclusion criteria (20 received HCQ, 47 LPV/RTV). [2] Groups were comparable regarding most baseline characteristics. Median time from symptom onset to treatment initiation was 8 days and was similar between the groups (p = 0.727). [3] There was no significant difference (HCQ vs. LPV/RTV) in hospital mortality (15% vs. 8.5%, p = 0.418), ICU admission rate (20% vs. 12.8%, p = 0.470) and length of stay (9 days vs. 11 days, p = 0.340). [4] A PCR negativity from nasopharyngeal swabs was observed in approximately two thirds of patients in both groups. [5] Side effects led to treatment discontinuation in 15% of patients in the LPV/RTV group.	[1] No statistically significant differences were observed in outcome parameters in patients treated with HCQ or LPV/RTV but patients in the LPV/RTV group showed a numerically lower hospital mortality rate. [2] Additionally, in comparison to other studies we demonstrated a lower mortality in patients treated with LPV/RTV despite having similar patient groups, perhaps due to early initiation of treatment.	높음	높음	높음	높음	높음	높음	높음	높음
	697	Faíco-Filho K.S (2020)	prospecitve observational study	66	HCQ : 66		[1] A total of 155 samples were collected from 66 patients with COVID-19 (60% female), with a median age of 58 years. The viral load between studied groups, assumed as a semiquantitative measure of cycle threshold (Ct) values, presented no significant difference within the three consecutive measures (ΔCt) (p > 0.05). [2] We also analyzed the ΔCt viral load at different intervals of sample collection (Δt < 7; 7–12; and > 12 days) without significant differences at any ΔCt (p > 0.05).	In this study, we did not observe any change in viral load reduction in vivo with the use of HCQ.	높음	높음	높음	높음	높음	높음	높음	높음
	724	Kelly M (2020)	retrospective analysis	134	HCQ + AZM: 82	52	[1] Data from a total of 134 patients were evaluated; 82 patients received HCQ/Az and 52 patients received no targeted therapy. [2] Clinical improvement was seen in 26.8% of patients who received HCQ/Az but this was not significant. [3] The rates of intensive care transfer and mechanical ventilation were higher in the treatment group, but these differences were not significant. [4] Mortality at day 28 was significantly higher in the treatment group (P = .03). [5] Hypoglycaemia elevated liver function tests and QT prolongation were monitored in both groups. [6] The risk of QT prolongation was significantly higher in the treatment group. Treatment was stopped early in 6 (7.3%) patients due to adverse events.	Although patients who received HCQ/Az were more severely ill the administration of these repurposed drugs did not result in clinical improvement and was associated with a significant increase in toxicity. This descriptive study highlights the importance of monitoring all repurposed agents for adverse events.	높음	높음	높음	높음	높음	높음	높음	높음
	921	Albani F (2020)	prospecitve observational study	1376	HCQ : 211, AZM : 421, HCQ + AZM : 166	605	[1] A logistic multivariate model with overlap weight propensity score was used for estimation of odds ratios (ORs) with 95% confidence intervals (95% CIs). [2] One thousand four hundred and three patients with SARS-CoV-2 infection were admitted to the hospital. [3] At the time of the analysis, the outcome was available for 1376 (98%) of them. [4] Five hundred and eighty-seven patients (42%) received azithromycin and 377 patients (27%) received hydroxychloroquine, alone or in combination. [5] In-hospital mortality was 26%. After the adjusted analysis, azithromycin alone was associated with lower mortality (OR 0.60, 95% CI 0.42–0.85) compared to no treatment. [6] Hydroxychloroquine alone (OR 0.76, 95% CI 0.53–1.08) and the combination of azithromycin and hydroxychloroquine (OR 1.13, 95% CI 0.77–1.69) were not associated with hospital mortality.	[1] In this cohort of patients, azithromycin alone was associated with lower hospital mortality but hydroxychloroquine was not associated with increased or reduced mortality. [2] While we await randomized clinical trials, these data support the use of azithromycin in novel coronavirus disease 2019 (COVID-19) and can contribute to better understanding of its role in further meta-analyses.	높음	높음	높음	높음	높음	높음	높음	높음

	1162	Roomi S (2020)	retrospecitve observational study	176	HCQ : 144, TCZ : 32	Non HCQ :	[1] The unadjusted odds ratio for patients upgraded to a higher level of care (ie, intensive care unit) (OR 2.6, 95% CI 1.19-5.69; P=.003) and reductions in C-reactive protein (CRP) level on day 7 of hospitalization (21% vs 56%, OR 0.21, 95% CI 0.08-0.55; P=.002) were significantly higher in the TCZ group compared to the control group. [2] There was no significant difference in the odds of in-hospital mortality, upgrade to intensive medical care, need for invasive mechanical ventilation, acute kidney failure necessitating dialysis, or discharge from the hospital after recovery in both the HCQ and TCZ groups compared to their respective control groups. [3] Adjusted odds ratios controlled for baseline comorbidities and medications closely followed the unadjusted estimates.	[1] In this cohort of patients with COVID-19, neither HCQ nor TCZ offered a significant reduction in in-hospital mortality, upgrade to intensive medical care, invasive mechanical ventilation, or acute renal failure needing dialysis. [2] These results are similar to the recently published preliminary results of the HCQ arm of the Recovery trial, which showed no clinical benefit from the use of HCQ in hospitalized patients with COVID-19 (the TCZ arm is ongoing). [3] Double-blinded randomized controlled trials are needed to further evaluate the impact of these drugs in larger patient samples so that data-driven guidelines can be deduced to combat this global pandemic.	음성	음성	음성	음성	음성	음성	음성	음성
	1235	Lecronier M (2020)	retrospective study	80	HCQ : 38, LPV/r : 20	SOC : 22	[1] Eighty patients were treated during a 4-week period and included in the analysis: 22 (28%) received standard of care only, 20 (25%) patients received lopinavir/ritonavir associated to standard of care, and 38 (47%) patients received hydroxychloroquine and standard of care. [2] Baseline characteristics were well balanced between the 3 groups. [3] Treatment escalation occurred in 9 (41%), 10 (50%), and 15 (39%) patients who received standard of care only, standard of care and lopinavir/ritonavir, and standard of care and hydroxychloroquine, respectively (p = 0.567). [4] There was no significant difference between groups regarding the number of ventilator-free days at day 28 and mortality at day 14 and day 28. [5] Finally, there was no significant change between groups in viral respiratory or plasma load between admission and day 7.	In critically ill patients admitted for SARS-CoV-2-related pneumonia, no difference was found between hydroxychloroquine or lopinavir/ritonavir as compared to standard of care only on the proportion of patients who needed treatment escalation at day 28. Further randomized controlled trials are required to demonstrate whether these drugs may be useful in this context.	음성	음성	음성	음성	음성	음성	음성	음성
	1387	Lagier J (2020)	Retrospective study	3737	HCQ + AZM over 3days : 3119	HCQ + AZM under 3d : 218, HCQ mono : 101, AZM mono : 137, Neither HCQ nor AZM : 161	[1] The patients' mean age was 45 (sd 17) years, 45% were male, and the case fatality rate was 0.9%. We performed 2,065 low-dose computed tomography (CT) scans highlighting lung lesions in 592 of the 991 (59.7%) patients with minimal clinical symptoms (NEWS score = 0). [2] A discrepancy between spontaneous dyspnoea, hypoxemia and lung lesions was observed. [3] Clinical factors (age, comorbidities, NEWS-2 score), biological factors (lymphocytopenia; eosinopenia; decrease in blood zinc; and increase in D-dimers, lactate dehydrogenase, creatinine phosphokinase, troponin and C-reactive protein) and moderate and severe lesions detected in low-dose CT scans were associated with poor clinical outcome. [4] Treatment with HCQ-AZ was associated with a decreased risk of transfer to ICU or death (Hazard ratio (HR) 0.18 0.11–0.27), decreased risk of hospitalization ≥10 days (odds ratios 95% CI 0.38 0.27–0.54) and shorter duration of viral shedding (time to negative PCR: HR 1.29 1.17–1.42). [5] QTc prolongation (>60 ms) was observed in 25 patients (0.67%) leading to the cessation of treatment in 12 cases including 3 cases with QTc> 500 ms. [6] No cases of torsade de pointe or sudden death were observed.	Although this is a retrospective analysis, results suggest that early diagnosis, early isolation and early treatment of COVID-19 patients, with at least 3 days of HCQ-AZ lead to a significantly better clinical outcome and a faster viral load reduction than other treatments.	음성	음성	음성	음성	음성	음성	음성	음성
	1408	Yu B (2020)	retrospecitve observational study	550	HCQ : 48	502	[1] We found that fatalities are 18.8% (9/48) in HCQ group, which is significantly lower than 47.4% (238/502) in the NHCQ group (P<0.001). The time of hospital stay before patient death is 15 (10–21) days and 8 (4–14) days for the HCQ and NHCQ groups, respectively (P<0.05). [2] The levels of inflammatory cytokine IL-6 were significantly reduced from 22.2 (8.3–118.9) pg mL–1 at the beginning of the treatment to 5.2 (3.0–23.4) pg mL–1 (P<0.05) at the end of the treatment in the HCQ group but there is no change in the NHCQ group.	These data demonstrate that addition of HCQ on top of the basic treatments is highly effective in reducing the fatality of critically ill patients of COVID-19 through attenuation of inflammatory cytokine storm. Therefore, HCQ should be prescribed as a part of treatment for critically ill COVID-19 patients, with possible outcome of saving lives.	음성	음성	음성	음성	음성	음성	음성	음성

	1519	Kalligeros M (2020)	observational matched cohort study	108	HCQ : 36 (HCQ + AZM: 32, HCQ mono : 4)	72	[1] 36 patients received hydroxychloroquine and were age- and sex-matched to 72 patients with COVID-19 who received supportive care. [2] Compared to supportive care, the use of HCQ did not shorten the time to clinical improvement (+0.23 days; 95% CI: −1.8–2.3 days) nor did it shorten the duration of hospital stay (+0.91 days; 95% CI: −1.1–2.9 days). [3] Additionally, HCQ did not decrease the risk of COVID-19 in-hospital death (aHR 1.67; 95% CI: 0.29–9.36). [4] Finally, we observed a slight QTc prolongation from a baseline of 444 ± 26 ms to 464 ± 32 ms (mean±SD) among patients receiving hydroxychloroquine with or without azithromycin.	This study did not yield benefits from hydroxychloroquine use in patients with COVID-19 and monitoring for adverse events is warranted. Nevertheless, the treatment was safely studied under the guidance of an antimicrobial stewardship program.	높음	높음	높음	높음	높음	높음	높음	높음

CQ3. 코로나19 환자에게 lopinavir/ritonavir 투여가 표준치료 혹은 무처치 대조군에 비하여 치료효과 및 안전성이 있는가? [RCT]

선행가이드라인 표시	문헌번호	1저자 (출판연도)	연구유형	대상자(N)	중재군(N)	비교/대조군(N)	연구결과	결론	Quality Assessment (ROB)					
									Randomization	allocation concealment	blinding of participants and personnel	blinding of outcome assessment	incomplete outcome data	selective outcome data
ACPG	50	Hongchao Pan (2020)	RCT	inpatients (11,330)	Remdesivir HQ L/R (1399) IFN beta 1a	no drugs (1372)	Death rate ratios (with 95% CIs and numbers dead/randomized, each drug vs its control). RR=1.00 (0.79-1.25, p=0.97; 148/1399 vs 146/1372)	lopinavir and Interferon regimens appeared to have little or no effect onhospitalized COVID-19, as indicated by overall mortality, initiation of ventilation and duration of hospital stay.	LOW	LOW	HIGH	LOW	LOW	LOW
ACPG	57	Yueping Li(2020)	RCT	mild to moderate (86)	L/R (34) arbidol (34)	no drugs (17)	* the rate of positive-to-negative conversion of SARS-CoV-2 nucleic acid, was similar between groups *no differences between groups in the secondary endpoints, the rates of antipyresis, cough alleviation, or improvement of chest computed tomography (CT) at days 7 or 14 * 12 (35.3%) patients in the LPV/r group and 5 (14.3%) in the arbidol group experienced adverse events during the follow-up period	LPV/r or arbidol monotherapy present little benefit for improving the clinical outcome of patients hospitalized with mild/moderate COVID-19 over supportive care.	LOW	LOW	LOW	LOW	LOW	LOW
ACPG, IDSA	58	Bin Cao (2020)	RCT	hospitalized severe adult (199)	L/R (99)	no drugs (100)	* Treatment with lopinavir-ritonavir was not associated with a difference from standard care in the time to clinical improvement (hazard ratio for clinical improvement, 1.31; 95% confidence interval [CI], 0.95 to 1.80). Mortality at 28 days was similar in the lopinavir-ritonavir group and the standard-care group (19.2% vs. 25.0%; difference, -5.8 percentage points; 95% CI, -17.3 to 5.7). The percentages of patients with detectable viral RNA at various time points were similar. * Gastrointestinal adverse events were more common in the lopinavir-ritonavir group, but serious adverse events were more common. Lopinavir-ritonavir treatment was stopped early in 13 patients (13.8%) because of adverse events.	no benefit was observed with lopinavir-ritonavir treatment beyond standard care	LOW	LOW	HIGH	LOW	LOW	LOW
ACPG	99	RECOVERY Collaborative Group (2020)	RCT	hospitalized pt (5040)	LPV/r (1616)	Usual care (3424)	374 (23%) patients allocated to lopinavir–ritonavir and 767 (22%) patients allocated to usual care died within 28 days (rate ratio 1·03, 95% CI 0·91–1·17; p=0·60) no significant difference in time until discharge alive from hospital (median 11 days [IQR 5 to >28] in both groups) or the proportion of patients discharged from hospital alive within 28 days (rate ratio 0·98, 95% CI 0·91–1·05; p=0·53) no significant difference in the proportion who met the composite endpoint of invasive mechanical ventilation or death (risk ratio 1·09, 95% CI 0·99–1·20; p=0·092)	In patients admitted to hospital with COVID-19, lopinavir–ritonavir was not associated with reductions in 28-day mortality, duration of hospital stay, or risk of progressing to invasive mechanical ventilation or death.	LOW	LOW	HIGH	LOW	LOW	LOW

CQ3. 코로나19 환자에게 lopinavir/ritonavir 투여가 표준치료 혹은 무처치 대조군에 비하여 치료효과 및 안전성이 있는가? [non-RCT]

선행가이드라인 표시	문헌번호	1저자 (출판연도)	연구유형	대상자(N)	중재군(N)	비교/대조군(N)	연구결과	결론	Quality Assessment (RoBANS)							
									대상자 비교가능성	대상자 선정	교란변수	노출측정	평가자의 눈가림	결과평가	불완전한 결과자료	선택적 결과보고
	#1	Gao 2020	retrospective review	non-sever e hospitalized pt (129)	LPV/r(53), chloroquine (19)	standard care (59)	The median duration of fever, median time fromsymptom onset to chest computer tomography improvement, andnegative conversion of the nucleic acid were similar among the 3groups. The median increase in cycle threshold values of N andORF1ab gene for patients receiving LPV/r or chloroquine or thestandard care during the treatment course was 7.0 and 8.5, 8.0, and7.6, 5.0, and 4.0, respectively. Thesefigures were not foundsignificantly different among the 3 groups.	Antiviral therapy using LPV/r or chloroquineseemed not to improve the prognosis or shorten the clinical courseof COVID-19.	높음	높음	높음	낮음	높음	낮음	낮음	낮음
	#466	Zhu 2020	retrospective review	hospitalized pt (50)	LPV/r(34)	Arbidol (16)	None of the patients developed severe pneumonia or ARDS.There was no difference infever duration between the two groups(P=0.61).On day14 after the admission,no viral load was detected in arbidol group, but the viral load was found in 15(44.1%) patients treated with lopinavir/ritonavir. Patients in the arbidol group had a shorter duration of positive RNA test compared to those in the lopinavir/ritonavir group(P<0.01).	arbidol monotherapy may be superior to lopinavir/ritonavir in treating COVID-19.	높음	높음	높음	낮음	높음	낮음	낮음	낮음
	#36	Grimaldi 2020	retrospective review	Moderate-to-severe ARDS (415)	LPV/r(57)	no antivirals (85) HQ (220) others (53)	none of the antiviral strategies increased the chance of being alive and weaned from MV at day 28 compared to the SOC strategy (OR 0.48 CI95% (0.18–1.25); OR 0.96 (0.47–2.02) and OR 1.43 (0.53–4.04) for L/R, OHQ and other treatments, respectively). Acute kidney injury dur‐ing ICU stay was frequent (55%); its incidence was higher in patients receiving lopinavir (66 vs 53%, P= 0.03). After adjustment for age, sex, BMI, chronic hypertension and chronic renal disease, the use of L/R was associated with an increased risk of renal replacement therapy (RRT). (OR 2.52 CI95% 1.16–5.59)	In this observational, multicentre, binational, study assessing moderate-to-severe ARDS complicating COVID-19 and requiring ICU admission in France and Belgium, we did not observe any benefit of antiviral ther-apies (L/R, OHQ or combination therapies).	낮음	낮음	낮음	높음	높음	낮음	낮음	낮음
	#21	Choi 2020	retrospective review	hospitalized pt (293)	Dz progression	Improvement	8 of 30 (60.0%) patientswho received lopinavir/ritonavir treatment showed disease progression, while 6 of 30 (20.0%) patientswho did not receive lopinavir/ritonavir treatment experienced disease progression. Patients treatedin the lopinavir/ritonavir group had significantly shorter PFS than that in the group not receivinglopinavir/ritonavir both before and after PS matching, but there was no significant difference in theproportion of discharged patients between the two groups.	Patients treated with lopinavir/ritonavir had significantly shorter progression-freesurvival than those not receiving lopinavir/ritonavir.	높음	높음	높음	높음	높음	높음	낮음	낮음
	#175	Yan 2020	retrospective review	non-critically ill admitted patients (120)	LPV/r (78)	usual care (42)	Viral shedding days 22 (18–29) vs. 28.5 (19.5–38) p=0.02 Hospital length of stay days 23 (19–27)vs. 18.5 (13–22.5) p<0.01	Older age and the lack of LPV/r treatment were independently associated with prolongedSARS-CoV-2 RNA shedding in patients with coronavirus disease 2019	높음	높음	높음	높음	높음	높음	높음	높음
	#294	Levy 2020	retrospective review	critical patients (42)	LPV/r (12)	SOC (30)	hepatotoxicity occurred more frequently in patients treated with lopinavir/ritonavir (33% vs 6.7%)	Caution is advised regarding the use of lopinavir/ritonavir in the most severe cases of Severe AcuteRespiratory Syndrome Coronavirus	낮음	높음	높음	높음	높음	낮음	낮음	낮음
	#168	Kim 2020	retrospective review	mild to moderate hospitalized pt (65)	LPV/r (31)	HQ (34)	Patients treated with lopinavir-ritonavir had a signifi-cantly shorter time to negative conversion of viral RNA than those treated with hydroxychloroquine (median, 21 days vs. 28 days). Treatment with lopinavir-ri-tonavir (adjusted hazard ratio [aHR], 2.28; 95% confidence interval [CI], 1.24 to 4.21) and younger age (aHR, 2.64; 95% CI 1.43 to 4.87) was associated with negative con-version of viral RNA. There was no significant difference in time to clinical im-provement between lopinavir-ritonavir- and hydroxychloroquine-treated patients (median, 18 days vs. 21 days). Lymphopenia and hyperbilirubinemia were more frequent in lopinavir-ritonavir-treated patients compared with hydroxychloro-quine-treated patients.	opinavir-ritonavir was associated with more rapid viral clearance than hydroxychloroquine in mild to moderate COVID-19, despite comparable clinical responses.	낮음	높음	높음	낮음	높음	낮음	낮음	낮음

#329	Zhang 2020	retrospective review	hospitalized pt (33)	Danoprevir(5)	LPV/r (28)	both negative nucleic acid testing and hospital stays of patients treatedwith danoprevir were significantly shorter than those of patients with lopinavir/ritonavir.	pplying danoprevir is a good treatment plan for COVID-19 patients.KEYWORDSCOVID-19, danoprevir, lopinavir/ritonavir, time to achieve negative nucleic acid testing1|INTRODUCTIONCoronavirus disease 2019 (COVID-19) is caused by a novel severeacute respiratory syndrome coronavirus (SARS-CoV-2), a causativeagent of a potentially fatal disease, and it has become a great globalpublic health concern.1From late 2019 to early 2020, the novelcoronavirus SARS-CoV-2 suddenly broke out among ordinary peo-ple in Wuhan, China, and rapidly spread in a short period of time.According to the data released by the World Health Organization(WHO), more than 2 540 000 cases were reported worldwide by23 April 2020, among which 175 000 patients died. The massiveoutbreak of COVID-19 has caused numerous casualties and a hugeeconomic loss. Therefore, it is vital to make effective treatmentplans as soon as possible and speed up the coordination of pre-vention and treatment, so as to protect people's health and reduceeconomic loss.	높음	높음	높음	높음	높음	낮음	높음	낮음
#393	Choi 2020	retrospective review (propensity score match)	mild-to-moderate hospitalized pt (4197)	LPV/r (1047) HQ (701)	SOC (1047) SOC(701)	he median viral shedding duration was 23 (IQR 17–32), 23 (IQR 16–32),and 18 (IQR 12–25) days in theLPV/r, HCQ, and control groups, respectively. Even after PSM, the viralshedding duration was not significantly different between LPV/r and HCQ groups: 23 (IQR, 17–32) days versus 23 (IQR, 16–32) days.	no benefit in viral agents groups	낮음	낮음	낮음	낮음	낮음	낮음	낮음	낮음
#92	Karolyi 2020	retrospective review	severe hospitalized pt (156)	HQ (20) LPV/r (47)	SOC (89)	There was no significant difference(HCQ vs. LPV/RTV) in hospital mortality (15% vs.8.5%,p= 0.418), ICU admission rate (20% vs. 12.8%,p= 0.470) and length of stay (9 days vs. 11 days,p= 0.340). A PCR negativity from nasopharyngealswabs was observed in approximately two thirds ofpatients in both groups. Side effects led to treatmentdiscontinuation in 15% of patients in the LPV/RTVgroup	No statistically significant differenceswere observed in outcome parameters in patientstreated with HCQ or LPV/RTV but patients in theLPV/RTV group showed a numerically lower hospitalmortality rate	낮음	높음	높음	낮음	높음	낮음	낮음	낮음

CQ4. 코로나19 환자에게 favipiravir, ribavirin, umifenovir, baloxavir marboxil 등 기타 바이러스 억제 효과가 있다고 알려진 약제의 투여가 표준치료 혹은 무처치 대조군에 비하여 치료효과 및 안전성이 있는가? [RCT]

선행가이드라인 표시	문헌번호	1저자 (출판연도)	연구유형	대상자 (N)	중재군(N)	비교/대조군 (N)	연구결과	결론	Quality Assessment (ROB)					
									Randomization	allocation concealment	blinding of participants and personnel	blinding of outcome assessment	incomplete outcome data	selective outcome data
ACPG	1	Lou Y (2020)	Open-label, exploratory	29	19 (baloxavir 10, favipiravir 9; plus other antivirals stated on the right)	10 (LPV/r or DRV/c + inhaled IFN-a)	Negative conversion @ D14 (primary): Baloxaxir 70%, favipiravir 77%, control 100% Time to clinical improvement (primary): Baloxavir 14 d, favipiravir 14 d, control 15 d	No significant difference in primary and secondary outcomes; study too small for conclusive results	Low	Low	High	High	High	High
ACPG	2	Ivashchenko AA (2020)	Phase I/II - dose finding	60	40 (favipiravir: high-dose 20, lowdose 20)	20	Negative conversion @ D10 (primary): favipiravir 92.5%, control 80.0% (p=0.155) Mortality (not predefined): favipiravir 2, control not reported ADR: favipiravir 17.5% (D/C 5.0%), control not reported	No meaningful clinical outcome reported; study too small and not designed for clinical efficacy	Low	Unclear	Unclear	Unclear	Low	Low
ACPG	3	Li Y (2020)	Exploratory	89	35	17; excluding 34 LPV/r group	Time to negative conversion: umifenovir 9.0 d, control 9.3 d (p=0.981) Clinical deterioration (secondary): umifenovir 8.6%, control 11.8% (p=0.206) ADR: umifenovir 14.3% (nausea/vomiting), control none	No significant difference in viral clearance and clinical outcome; study too small and designed as an exploratory study	Low	Low	Low	Low	High	High
ACPG	4	Yethindra V (2020)	Exploratory	30	15 (umifenovir)	15	Time to fever resolution: umifenovir 2.4 d, control 3.3 d Time to cough resolution: umifenovir 2.1 d, control 3.2 d Mortality or severe disease: none	No meaningful clinical outcome reported; study too small and not designed for clinical efficacy	Low	Unclear	Unclear	Unclear	High	High
ACPG	5	Chen C (2020)	Open-label, multicenter	240	favipiravir 116: umifenovir 120		Clinical recovery @ D7 (primary): favipiravir 61.2%, umifenovir 51.7% (p=0.140) Clinical recovery among moderate pt (post-hoc): favipiravir 71.4%, umifenovir 55.9% (p=0.020) Oxygen or NMV: favipiravir 18.1%, umifenovir 22.5% (p=0.402)	No significant difference in primary outcome; study did not include SOC as control	Low	Low	High	High	High	High
BC	6	Hung (2020)	Open-label, multicenter	127	86 (ribavirin + LPV/r + IFN-b1b)	41 (LPV/r)	Time to negative conversion (primary): combination 7 d, control 12 d (p=0.001) Clinical improvement (symptoms, NEWS2, SOFA): significantly faster in combination group No difference in critical care or mortality	Significant benefit observed w/ combination therapy; unclear which of the agent (IFN or ribavirin) was the reason	Low	Low	High	High	High	High
BC	7	Kasgari (2020)	Open-label	48	24 (ribavirin + sofosbuvir/daclatasvir)	24 (SOC)	Length of hospital stay (primary): 6 d for both (p=0.398) ICU admissions: intervention 0, control 4 (p=0.109) Mortality: intervention 0, control 3 (p=0.234)	No benefit or harm observed; too small to draw conclusion; baseline characteristics were not balanced	Low	Low	High	High	High	High
	8	Doi (2020)	Open-label, multicenter	69	36 (early)	33 (late)	Viral clearance @ D6 (primary): early 66.7%, late 56.1% (p=0.308) Time to defervescence: early 2.1 d, late 3.2 d (=0.048)	No relevant clinical outcome tested; small number	Low	Low	High	High	High	High
	221	Huang (2020)	Open-label, single center	101	33 ribavirin + IFN-a, 36 LPV/r + IFN-a, 32 ribavirin + LPV/r + IFN-a		Time to negative conversion: 13 d, 12 d, 15 d (p=0.42) Mortality: 0%, 0%, 0%	No significant differences in time to PCR negativity; clinical outcome (mortality) not occurred; ADR more commonly observed in RBV+LPV/r; no SOC as control	Low	Low	High	High	Low	Low

CQ4. 코로나19 환자에게 favipiravir, ribavirin, umifenovir, baloxavir marboxil 등 기타 바이러스 억제 효과가 있다고 알려진 약제의 투여가 표준치료 혹은 무처치 대조군에 비하여 치료효과 및 안전성이 있는가? [non-RCT]

선행가이드라인 표시	문헌번호	1저자(출판연도)	연구유형	대상자(N)	중재군(N)	비교/대조군(N)	연구결과	결론	Quality Assessment (RoBANS)							
									대상자비교가능성	대상자선정	교란변수	노출측정	평가자의 눈가림	결과평가	불완전한 결과자료	선택적 결과보고
BC	1	Yuan (2020)	2	94	21 (IFN-a + LPV/r + ribavirin)	46 (IFN-a + LPV/r)	No significant difference in hospital stay or PCR negative conversion		Low	High	High	Low	Low	Low	High	High
BC	2	Eslami (2020)	1	62	27 (ribavirin + LPV/r + HCQ)	35 (sofosbuvir/daclatasvir + LPV/r + HCQ)	Length of hospital stay (primary): RBV 9 d, SOF/DCV 5 d (p<0.01) ICU admission (2ndary): RBV 48%, SOF/DCV 17% (p=0.01) Mortality (2ndary): RBV 33%, SOF/DCV 5.7% (p=0.01)	SOF/DCV significantly better than RBV; however, the trial did not include SOC as control	High	Low	High	Low	Low	Low	Low	Low
	3	Cai (2020)	1	80	35 (favipiravir + inhaled IFN-a)	45 (LPV/r + inhaled IFN-a)	Time to negative conversion: FPV 4 d, LPV/r 11 d (p<0.001) Improvement of chest CT: FPV 91.4%, LPV/r 62.2% (p=0.004)	Clinical outcome was not observed; too small for conclusive results; no SOC as control	High	Low	High	Low	High	High	Low	Low
	4	Zhu (2020)	2	50	16 (umifenovir)	34 (LPV/r)	PCR negative @ D14: umifenovir 100%, LPV/r 55.9% (p<0.01)	Clinical outcome was not observed; too small for conclusive results; no SOC as control; imbalance in baseline characteristics	High	Low	High	Low	Low	Low	Low	Low
	5	Deng (2020)	2	33	16 (umifenovir + LPV/r)	17 (LPV/r)	PCR negative @ D7: combination 75%, LPV/r 35% (P<0.05) CT improvement: combination 69%, LPV/r 29% (p<0.05)	Clinical outcome was not observed; too small for conclusive results; no SOC as control	High	Low	High	Low	High	High	Low	Low
	6	Lian (2020)	2	81	45 (umifenovir)	36	PCR negative @ D7: umifenovir 73%, control 78% (p=0.19) No death in both groups	Clinical outcome was not observed	High	Low	High	Low	Low	Low	Low	Low
	7	Chen (2020)	2	62	42 (umifenovir)	20	Faster resolution of fever and dry cough	Relevant clinical outcome omitted	High	Low	High	Low	High	High	High	High
	89	Tong (2020)	2	115	44 (ribavirin)	71 (SOC)	Time to negative conversion: ribavirin 12.8 d, control 14.1 d (p=0.314) Mortality: ribavirin 17.1%, control 24.6% (p=0.475)	No significant difference in both negative conversion of PCR and mortality; study underpowered	High	Low	High	Low	High	Low	Low	Low
	42	Fang (2020)	2	162	63 (umifenovir + lianhuaqingwen)	99 (lianhuaqingwen only)	Time to negative conversion was significantly shorter in combination therapy among pts w/ moderate COVID-19, but not those w/ severe disease; no difference in mortality	The main findings rely heavily on post-hoc subgroup analyses; no difference in clinical outcome	High	Low	High	Low	High	High	Low	High
	36	Kocayiğit (2020)	Unclear	107	65 (favipiravir + HCQ)	42 (LPV/r + HCQ)	Mortality: favipiravir 66.2%, LPV/r 54.8% (p=0.237) ICU LOS: favipiravir 6.6 d, LPV/r 9 d (p=0.010)	Similar mortality with different ICU LOS is difficult to interpret; FPV was used in the later course of epidemic, following change in the local guideline	High	Low	High	Low	High	Low	Low	High
	50	Gao (2020)	2	220	130 (umifenovir)	90	Umifenovir-including regimen was associated with faster resolution of fever (p=0.044), PCR negative @ D14 (p=0.028)	Multiple other agents were used in both groups; significant imbalance in baseline characteristics; no clinically relevant outcome observed	Low	High	High	Low	High	High	High	High

CQ5. 코로나19 환자에게 스테로이드 투여가 표준치료 혹은 무처치 대조군에 비하여 치료효과 및 안전성이 있는가? [RCT]

선행가이드라인 표시	문헌번호	1저자(출판연도)	연구유형	대상자(N)	중재군(N)	비교/대조군(N)	연구결과	결론	Quality Assessment (ROB)						
									Randomization	allocation concealment	blinding of participants and personnel	blinding of outcome assessment	incomplete outcome data	selective outcome data	
IDSA/ACPG	69/33	Horby (2020)	open-label	6425	dexamethasone (2104)	usual care. (4321)	28d mortality, dexa vs usual care in receiving invasive MV 29.3% vs. 41.4%; rate ratio, 0.64; 95% CI, 0.51 to 0.81 in receiving oxygen 23.3% vs. 26.2%; rate ratio, 0.82; 95% CI, 0.72 to 0.94 in receiving no respiratory support 17.8% vs. 14.0%; rate ratio, 1.19; 95% CI, 0.91 to 1.55	lower 28-day mortality among those who were receiving either invasive mechanical ventilation or oxygen alone at randomization but not among those receiving no respiratory support.	low	low	high	low	low	low	low
IDSA/ACPG	70/29	Tomazini (2020)	open-label	299	dexamethasone (151)	standard care (148)	IV dexa vs standard alone in mod or severe ARDS COVID-19 pts: 6.6 ventilator free days vs 4.0 ventilator free days during the first 28days (difference, 2.26; 95% CI, 0.2-4.38; P = 0.04) SOFA 6.1 vs 7.5 (difference, -1.16; 95% CI, -1.94 to -0.38; P = .004) No different 2nd outcomes : all-cause mortality at 28 days, ICU-free days during the first 28 days, mechanical ventilation duration at 28 days, or the 6-point ordinal scale at 15 days.	moderate or severe ARDS, use of IV dexamethasone + standard care compared with standard care alone : statistically significant increase in the number of ventilator-free days (days alive and free of mechanical ventilation) over 28 days.	low	low	low	low	low	low	
IDSA/ACPG	71/26	Dequin (2020)	double-blind sequential	149	low-dose hydrocortisone (76)	placebo(73)	treatment failure on day 21, 32/76 patients (42.1%) in the hydrocortisone group vs. 37/73 (50.7%) in the placebo group (difference of proportions, -8.6% [95.48% CI, -24.9% to 7.7%]; P = .29)	in critically ill patients with COVID-19 and acute respiratory failure: low-dose hydrocortisone, compared with placebo, did not significantly reduce treatment failure (defined as death or persistent respiratory support) at day 21	low	low	low	low	low	unclear	
IDSA/ACPG	72/28	Angus(2020)	open-label	384	fixed 7-day course of IV hydrocortisone (50mg or 100mg q6h) (137)	shock-dependent course (hyprocortisone 50mg q6h) (146) or no hydrocortisone (101)	fixed 7d vs no steroid : 1.43 (ORs) and 93% bayesian probability) shock-dependent vs no steroid : 1.22 (Ors) and 80% (bayesian probability)	steroid use (fixed and shock-dependent): 93% and 80% probabilities of superiority with regard to the odds of improvement in organ support-free days within 21 days. Early stopped	low	low	high	low	low	unclear	other risk high
ACPG	32	Jeronimo (2020)	double-blind, Phase IIb, placebo-controlled	393	IV methylprednisolone(0.5mg/kg for 5dys) (194)	placebo(199)	28d mortality, MP vs placebo : no deference (37.1% vs 38.2%) subgroup (over 60yrs) : MP vs placebo 28d mortality 46.6% vs 61.9% P=0.039 MP arm tended to need more insulin therapy, and no difference in viral clearance in respiratory secretion until D7	short course of MP in hospitalized patients with COVID-19 did not reduce mortality in the overall population.	low	low	low	low	high	low	

CQ5. 코로나19 환자에게 스테로이드 투여가 표준치료 혹은 무처치 대조군에 비하여 치료효과 및 안전성이 있는가? [non-RCT]

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									대상자비교 가능성	대상자 선정	교란변수	노출측정	평가자의 눈가림	결과평가	불완전한 결과자료	선택적 결과보고
IDSA/NIH	68/20	WHO REACT (2020)	Meta	1703	systemic dexamethasone, hydrocortisone, or methylprednisolone (678 patients)	usual care or placebo (1025 patients).	steroid vs placebo : Death 222/678 vs 425/1025 (OR 0.66 95CI 0.53-0.82, P < .001) The fixed-effect summary OR for the association with mortality: Dexa : 0.64 (95% CI, 0.50-0.82; P < .001) (3 trials, 1282 pts, 527 deaths) Hydroco : 0.69 (95% CI, 0.43-1.12; P = .13) (3 trials, 374 pts, 94 deaths) MP: 0.91 (95% CI, 0.29-2.87; P = .87) (1 trial, 47 pts, 26 deaths)	administration of systemic corticosteroids, compared with usual care or placebo, was associated with lower 28-day all-cause mortality.								
NIH	28	Li (2020)	retrospective cohort	475	early, low-dose steroid(55) : IV MP 20mg/d or 40mg/d for 3-5d (50) prednisone 30mg/d for 3d (5)	no steroid use (420)	Primary outcomes :steroid vs control severe disease development : 12.7% vs 1.8% (p=0.028) Death: 1pt vs 0 pt 2ndary outcomes: steroid vs control duration of fever : 5ds vs 3ds viral clearance time : 18ds vs 11ds length of hospital stay 23ds vs 15ds (P <0.001 for each)	In adult patients with non-severe COVID-19 pneumonia, early, low-dose, and short-term corticosteroids therapy was associ- ated with worse clinical outcomes.	low	low	high	high	high	low	high	low
	132	Ruiz-Irastorza (2020)	observational study	242	1mg/kg/d several dasy as 1st week, and at 2nd week, MP pulse 3d (125-250mg/d) (61)	out of-week-2-MP or non-pulse or no steroid use (181)	Adjusted HRs (death) : week-2-MP 0.35 (P=0.064) in wholde cohort, 0.31 (P=0.073) in lower SpO2/FiO2 353 (n=122)	Week-2-MP are effective in improving the prognosis of patients with COVID-19 pneumonia with features of inflammatory activity and respiratory deterioration entering the second week of disease.	high	low	high	high	high	low	high	low
	244	Majmundar (2020)	single-center retrospective cohort	205	steroid (60)	no steroid use (145)	Primary outcomes: composite outcome of ICU transfer, intubation , in-hostpital mortaliry steroid vs non-steroid 13 (22.41%) vs. 54 (37.50%) P= 0.039 adjusted HR 0.15 (P<0.001)	Among non-ICU patients hospitalized with COVID-19 pneumonia, treatment with corticosteroid was associated with a significantly lower risk of the primary composite outcome of ICU transfer, intubation, or in-hospital death	low	low	high	high	high	low	unclear	low
	565	Bartoletti (2020)	Multicenter observational study	513	steroid (170)	no steroid use (343)	multivariable analysis: steroid treatment was not associate dwith lower 30d mortality rate (OR 0.59 P=0.33) subgroup analysis: in patients with P/F <200 at admission (135 patients, 53(38%) with steroid) steroid treatment was associated with a lower risk of 30d mortality (44% vs 54% OR 0.20 P=0.036)	The effect of corticosteroid treatment on mortality might be limited to critically ill COVID-19 patients.	high	low	low	high	high	low	high	high

CQ6. 코로나19 환자에게 tocilizumab이나 이와 유사한 IL-6 억제제 투여가 표준치료 혹은 무처치 대조군에 비하여 치료효과 및 안전성이 있는가? [RCT]

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									Randomization	allocation concealment	blinding of participants and personnel	blinding of outcome assessment	incomplete outcome data	selective outcome data
IDSA, ACPG	89	Rosas (2020)	Randomized (2:1) to double-blinded	438	N=294; tocilizumab (8 mg/kg) +/- steroids(36.1%), antivirals(29.6%), convalesent(3.4%)	N=144; steroids (54.9%), antivirals (35.4%), and convalescent plasma (4.2%)	28-day mortality compared to no tocilizumab treatment (RR: 0.80; 95% CI: 0.54, 1.19); no difference in the primary outcome of day 28 clinical status (as assessed on an ordinal scale) between the tocilizumab and placebo groups (OR 1.19, 95% CI 0.81, 1.76), but patients were more likely to be discharged earlier from the hospital (HR: 1.35; 95% CI: 1.02, 1.79; Low CoE).	Tocilizumab did not improve clinical status or mortality. Potential benefits in time to hospital discharge and duration of ICU stay are being investigated in ongoing clinical trials	Low	Low	Low	Low	Low	Low
ACPG	180	Wang (2020)	Randomized, controlled, open-label, multicenter trial	65	N=33; tocilizumab in addition to standard care	N=32; standard care	The cure rate in tocilizumab group was higher than that in the controls but not significant (94.12% vs 87.10%, P=0.4133). Adverse events were recorded in 20 (58.82%) of 34 tocilizumab recipients versus 4 (12.90%) of 31 in the controls. No serious adverse events were reported in tocilizumab group.	Tocilizumab treatment did not increase the cure rate of COVID-19. However , tocilizumab can improve oxygenation without significant influence on the time virus load tunes negative. For patients with bilateral pulmonary lesions and elevated IL-6 levels, tocilizumab should be recommended for better disease management.	Low	High	High	High	Low	Low
ACPG	185	Hermine (2020)	Cohort-embedded, investigator-initiated, multicenter, open-label, bayesian randomized clinical trial	131	N=64; IV tocilizumab plus usual care	N=67; usual care (antibiotic agents, antiviral agents, corticosteroids, vasopressor support, and anticoagulants)	In the TCZ group, 12 patients had a WHO-CPS score greater than 5 at day 4 vs 19 in the UC group (median posterior absolute risk difference [ARD] -9.0%; 90% credible interval [CrI], -21.0 to 3.1), with a posterior probability of negative ARD of 89.0% not achieving the 95% predefined efficacy threshold. At day 14, 12% (95% CI -28% to 4%) fewer patients needed noninvasive ventilation (NIV) or mechanical ventilation (MV) or died in the TCZ group than in the UC group (24% vs 36%, median posterior hazard ratio [HR] 0.58; 90% CrI, 0.33-1.00), with a posterior probability of HR less than 1 of 95.0%, achieving the predefined efficacy threshold. The HR for MV or death was 0.58 (90% CrI, 0.30 to 1.09). At day 28, 7 patients had died in the TCZ group and 8 in the UC group (adjusted HR, 0.92; 95% CI 0.33-2.53). Serious adverse events occurred in 20 (32%) patients in the TCZ group and 29 (43%) in the UC group (P = .21).	In this randomized clinical trial of patients with COVID-19 and pneumonia requiring oxygen support but not admitted to the intensive care unit, TCZ did not reduce WHO-CPS scores lower than 5 at day 4 but might have reduced the risk of NIV, MV, or death by day 14. No difference on day 28 mortality was found.	Low	High	High	High	Low	Low
ACPG	186	Stone (2020)	Randomized, double-blind, placebo-controlled trial	243	N=161; tocilizumab (8 mg per kilogram of body weight) plus standard care	N=81; standard care	The hazard ratio for intubation or death in the tocilizumab group as compared with the placebo group was 0.83 (95% confidence interval [CI], 0.38 to 1.81; P = 0.64), and the hazard ratio for disease worsening was 1.11 (95% CI, 0.59 to 2.10; P = 0.73). At 14 days, 18.0% of the patients in the tocilizumab group and 14.9% of the patients in the placebo group had had worsening of disease. The median time to discontinuation of supplemental oxygen was 5.0 days (95% CI, 3.8 to 7.6) in the tocilizumab group and 4.9 days (95% CI, 3.8 to 7.8) in the placebo group (P = 0.69). At 14 days, 24.6% of the patients in the tocilizumab group and 21.2% of the patients in the placebo group were still receiving supplemental oxygen. Patients who received tocilizumab had fewer serious infections than patients who received placebo.	Tocilizumab was not effective for preventing intubation or death in moderately ill hospitalized patients with Covid-19. Some benefit or harm cannot be ruled out, however, because the confidence intervals for efficacy comparisons were wide.	Low	Low	Low	Low	Low	Low

	#276	Salvarani (2020)	Prospective, open-label, randomized clinical trial	123	N=60; intravenous tocilizumab within 8 hours from randomization (8 mg/kg up to a maximum of 800 mg), followed by a second dose after 12 hours	N=63; supportive care	Seventeen patients of 60 (28.3%) in the tocilizumab arm and 17 of 63 (27.0%) in the standard care group showed clinical worsening within 14 days since randomization (rate ratio, 1.05; 95% CI, 0.59-1.86). Two patients in the experimental group and 1 in the control group died before 30 days from randomization, and 6 and 5 patients were intubated in the 2 groups, respectively.	In this randomized clinical trial of hospitalized adult patients with COVID-19 pneumonia and Pao2/Fio2 ratio between 200 and 300 mm Hg who received tocilizumab, no benefit on disease progression was observed compared with standard care.	Low	Low	High	High	Low	Low

CQ6. 코로나19 환자에게 tocilizumab이나 이와 유사한 IL-6 억제제 투여가 표준치료 혹은 무처치 대조군에 비하여 치료효과 및 안전성이 있는가? [non-RCT]

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									대상자비교가능성	대상자선정	교란변수	노출측정	평가자의 눈가림	결과평가	불완전한 결과자료	선택적 결과보고
NIH	8	Sciascia (2020)	prospective, open-label study	63	tocilizumab (8 mg/kg) IV or tocilizumab (324 mg) SQ	None	Following administration of tocilizumab, fevers resolved in all but one patient, and CRP, ferritin, and D-dimer levels declined. No moderate or severe adverse events attributable to tocilizumab were reported. The authors report an association between earlier use of tocilizumab and reduced mortality.		-	Low	Low	Low	High	High	High	Low
IDSA	93	Montesarchio (2020)	Retrospective case series	15	Sarilumab	None	Among 10 patients whose symptoms improved after sarilumab treatment, rapid decreases in CRP levels corresponded with clinical improvement. Lower levels of IL-6 at baseline as well as lower neutrophil to lymphocyte ratio as compared with patients whose COVID-19 did not improve with treatment were associated with sarilumab-responsive disease	This observation may reflect a possible clinical benefit regarding early intervention	-	High	High	Low	High	High	High	Low
IDSA	85	Guaraldi (2020)	Retrospective, observational cohort study	90	N=57; tocilizumab, 8 mg/kg bodyweight (up to a maximum of 800 mg) in two infusions, 12 h apart, or subcutaneously at 162 mg administered in two simultaneous doses, one in each thigh (ie, 324 mg in total)	N=33; Standard of care (ie, supplemental oxygen, hydroxychloroquine, azithromycin, antiretrovirals, and low molecular weight heparin)	73 (20%) patients in the standard care group died, compared with 13 (7%; p<0·0001) patients treated with tocilizumab. tocilizumab treatment was associated with a reduced risk of invasive mechanical ventilation or death (adjusted hazard ratio 0·61, 95% CI 0·40-0·92; p=0·020). 24 (13%) of 179 patients treated with tocilizumab were diagnosed with new infections, versus 14 (4%) of 365 patients treated with standard of care alone (p<0·0001).	Treatment with tocilizumab, whether administered intravenously or subcutaneously, might reduce the risk of invasive mechanical ventilation or death in patients with severe COVID-19 pneumonia.	High	High	Low	High	High	High	Low	Low
IDSA	86	Campochiaro (2020)	Retrospective study	65	N=32; intravenous TCZ in addition to standard of care	N=33; standard of care alone	69% of TCZ patients experienced a clinical improvement compared to 61% of standard treatment patients (p = 0.61). Mortality was 15% in the tocilizumab group and 33% in standard treatment group (p = 0.15). The rate of infection and pulmonary thrombosis was similar between the two groups.	At day 28, clinical improvement and mortality were not statistically different between tocilizumab and standard treatment patients in our cohort. Bacterial or fungal infections were recorded in 13% of tocilizumab patients and in 12% of standard treatment patients.	High	High	High	High	High	High	High	Low
IDSA	87	Kewan (2020)	Retrospective cohort study	51	N=28; tocilizumab in addition to standard of care (steroid, hydroxychloroquine, or azithromycin)	N=23; standard of care (steroid, hydroxychloroquine, or azithromycin)	The median time to clinical improvement in tocilizumab vs. no tocilizumab cohorts was 8 days (Interquartile range [IQR]: 6·25 - 9·75 days) vs. 13 days (IQR: 9·75 - 15·25 days) among patients who required mechanical ventilation at any time (Hazard ratio for clinical improvement: 1·83, 95% confidence interval [CI]: 0·57 - 5·84) and 6·5 days vs. 7 days among all patients (Hazard ratio for clinical improvement: 1·14, 95% CI: 0·55 - 2·38), respectively. The median duration of vasopressor support and invasive mechanical ventilation were 2 days (IQR: 1·75 - 4·25 days) vs. 5 days (IQR: 4 - 8 days), p = 0.039, and 7 days (IQR: 4 - 14 days) vs. 10 days (IQR: 5 - 15 days) in tocilizumab vs. no tocilizumab cohorts, p = 0.11, respectively. Similar rates of hospital-acquired infections occurred in both cohorts (18% in tocilizumab and 22% in no tocilizumab cohort).	In patients with severe COVID-19, tocilizumab was associated with significantly shorter duration of vasopressor support. Although not statistically significant, tocilizumab also resulted in shorter median time to clinical improvement and shorter duration of invasive ventilation.	High	High	High	High	High	High	High	Low
IDSA	88	Rossi (2020)	Retrospective cohort study	158	N=90; tocilizumab once (either 400 mg intravenous or 324 mg subcutaneous) in addition to standard of care	N=68; standard protocol (hydroxychloroquine 400 mg daily, lopinavir 800 mg plus ritonavir 200 mg per day)	Tocilizumab significantly improved survival compared to standard care (multivariate HR: 0.057; 95% C.I = 0.017- 0.187, p < 0.001). No tocilizumab-related infections and/or side effects were observed.	Early treatment with tocilizumab could be helpful to prevent excessive hyper-inflammation and death in COVID-19 related pneumonia. Low dose administration of tocilizumab is not associated with adverse events.	High	High	High	High	High	High	High	High

	#310	Gupta (2020)	Multicenter cohort study	3924	N=433; tocilizumab in the first 2 days of admission to the ICU	N=3491; Those who did not receive tocilizumab in the first 2 days of admission to the ICU	In the primary analysis, during a median follow-up of 27 (IQR, 14-37) days, patients treated with tocilizumab had a lower risk of death compared with those not treated with tocilizumab (HR, 0.71; 95% CI, 0.56-0.92). The estimated 30-day mortality was 27.5% (95% CI, 21.2%-33.8%) in the tocilizumab-treated patients and 37.1% (95% CI, 35.5%-38.7%) in the non-tocilizumab-treated patients (risk difference, 9.6%; 95% CI, 3.1%-16.0%).	Among critically ill patients with COVID-19 in this cohort study, the risk of in-hospital mortality in this study was lower in patients treated with tocilizumab in the first 2 days of ICU admission compared with patients whose treatment did not include early use of tocilizumab.	High	High	High	High	High	Low	Low	Low
	#268	Biran (2020)	Multicentre observational study	630	N=210; who received tocilizumab	N=420; who did not receive tocilizumab	Overall median survival from time of admission was not reached (95% CI 23 days-not reached) among patients receiving tocilizumab and was 19 days (16-26) for those who did not receive tocilizumab (hazard ratio [HR] 0·71, 95% CI 0·56-0·89; p=0·0027). Cox regression analysis with propensity matching, an association was noted between receiving tocilizumab and decreased hospital-related mortality (HR 0·64, 95% CI 0·47-0·87; p=0·0040)	patients with COVID-19 requiring ICU support who received tocilizumab had reduced mortality	High	High	High	Low	High	Low	Low	Low
	#162	Martinez-Sanz (2020)	Multicentre cohort study	1229	N=261; tocilizumab group	N=969; control group	Tocilizumab was associated with decreased risk of death (adjusted hazard ratio 0.34, 95% confidence interval 0.16-0.72, p 0.005) and ICU admission or death (adjusted hazard ratio 0.39, 95% confidence interval 0.19-0.80, p 0.011) among patients with baseline CRP >150 mg/L but not among those with CRP ≤150 mg/L.	Tocilizumab was associated with a lower risk of death or ICU admission or death in patients with higher CRP levels	High	High	High	Low	High	Low	Low	Low
	#234	Chilimuri (2020)	Retrospective cohort study	1225	N=87; who received tocilizumab	N=1138; who did not receive tocilizumab	The risk of intubation or death was significantly lower among patients who received tocilizumab compared to patients who did not (hazard ratio, 0.40; 95% CI, 0.20-0.77).	A possible benefit with tocilizumab treatment in patients with moderate to severe COVID-19 in preventing disease progression to respiratory failure.	High	High	High	High	High	High	High	Low
	#312	Rodriguez-bano (2020)	Multicenter cohort study	778	N=88; tocilizumab	N=117, 78, 151; intermediate-high dose of corticosteroids (IHDC), a pulse dose of corticosteroids (PDC), combination therapy	The IPTW-based hazard ratios (odds ratio for combination therapy) for the primary endpoint were 0.32 (95%CI 0.22-0.47; p < 0.001) for tocilizumab, 0.82 (0.71-1.30; p 0.82) for IHDC, 0.61 (0.43-0.86; p 0.006) for PDC, and 1.17 (0.86-1.58; p 0.30) for combination therapy.	Tocilizumab might be useful in COVID-19 patients with a hyperinflammatory state.	High	High	High	Low	High	Low	Low	Low

CQ7. 코로나19 환자에게 IL-1 억제제 투여가 표준치료 혹은 무처치 대조군에 비하여 치료효과 및 안전성이 있는가? [non-RCT]

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									대상자비교가능성	대상자선정	교란변수	노출측정	평가자의 눈가림	결과평가	불완전한 결과자료	선택적 결과보고
Jin et al	1	Huet (2020)	Cohort-retrospective	severe COVID-19	52	44	*Anakinra, SQ at a dose of 100 mg twice daily for 3 days, then 100 mg daily for 7 days * Significant reduction on the need for invasive mechanical ventilation or death in the multivariate analysis: anankinra (25%) vs. control group (73%) (HR = 0.22, 95% CI 0.10–0.49, P = 0.0002) * Frequency of elevated liver enzymes, coagulopathy was similar between patients in anakinra (13%) and control (9%) * No increase in bacterial infection	Anakinra reduced both need for invasive mechanical ventilation in the ICU and mortality among patients with severe forms of COVID-19, without serious side-effects.	낮음	낮음	높음	낮음	높음	낮음	높음	낮음
Jin et al	2	Cavali (2020)	Cohort-retospective	COVID-19, moderate-severe ARDS, hyperinflammation and on non-invasive ventilation outside of ICU	29 (high dose)	16	* Anakinra IV at a 5mg/kg twice a day (high dose) or SQ 100 mg twice a day (low dose) * Comparison only between high dose and control group * Higher survival in high dose anakinra group at 21 days (90% vs. 56%, P = 0.009) * Incidence of bacteremia, increased liver enzymes, and thromboembolism was similar in the two groups * Bacteremia in high dose anakinra group (14% and control group (13%)	In patients with COVID-19 and ARDS managed with non-invasive ventilation outside of the ICU, treatment with high-dose anakinra was safe and associated with clinical improvement in 72% of patients	낮음	낮음	높음	낮음	높음	낮음	높음	낮음
	3	Langer-Gould, A (2020)	Cohort-retospective	COVID-19 with cytokine storm	41	52 (tocilizumab)	* High-dose anakinra (100 mg SQ every 6 h; or every 12 h for those with renal failure) * Tocilizumab (n = 52): 50 (96.2%) were intubated, and only seven (13.5%) received concomitant corticosteroids. * Anakinra group (n = 41): 23 (56.1%) were intubated, and all received concomitant corticosteroids. * Fewer anakinra-treated patients died (n = 9, 22%) and more were extubated/never intubated (n = 26, 63.4%) compared to tocilizumab-treated patients (n = 24, 46.2% dead, n = 22, 42.3% extubated/never intubated). * After accounting for differences in disease severity at treatment initiation, superiority of anakinra over tocilizumab was no longer statistically significant (propensity scoreadjusted hazards ratio 0.46, 95% confidence interval 0.18–1.20).	Prompt identification and treatment of COVID19-CS before intubation may be more important than the specific type of anti-inflammatory treatment.	낮음	낮음	높음	낮음	높음	낮음	높음	낮음
	4	Cauchois (2020)	Cohort-retrospective	COVID-19 with pneumonia	12	10	* Anakinra: IV over 2h once daily 300 mg/day for 5 days, then tapered to 200 mg/day for 2 days and hen 100 mg * All of patients treated with anakinra improved clinically (P < 0.01), with no deaths, significant decreases in oxygen requirements (P < 0.05), and more days without invasive mechanical ventilation (P < 0.06), compared with the control group. * The effect of anakinra was rapid, as judged by significant decrease of fever and C-reactive protein at day 3. * No adverse side effects or bacterial infection.	E early blockade of the IL-1 receptor is therapeutic in acute hyperinflammatory respiratory failure in COVID- 19 patients.	낮음	낮음	높음	낮음	높음	낮음	높음	낮음
	5	Narain (2020)	Cohort retrospective	COVID-19, hospiltalized	Anakinra only (57); Steroid + Anakinra (N=733)	Standard care (N=3,076); Steroid only (N=1,383); Steroid + Tocilizumab (N=454); Tocilizumab only (N=73)	* Patients treated with corticosteroids and tocilizumab combination showed lower mortality compared with patients receiving standard-of-care (SoC) treatment (hazard ratio [HR], 0.44; 95% CI, 0.35-0.55; P < .0001) and with patients treated with corticosteroids alone (HR, 0.66; 95% CI, 0.53-0.83; P ¼ .004) or in combination with anakinra (HR, 0.64; 95% CI, 0.50-0.81; P ¼ .003). * Corticosteroids when administered alone (HR, 0.66; 95% CI, 0.57-0.76; P < .0001) or in combination with tocilizumab (HR, 0.43; 95% CI, 0.35-0.55; P < .0001) or anakinra (HR, 0.68; 95% CI, 0.57-0.81; P < .0001) improved hospital survival compared with SoC treatment.	The combination of corticosteroids with tocilizumab showed superior survival outcome when compared with SoC treatment and treatment with corticosteroids alone or in combination with anakinra.	낮음	낮음	높음	낮음	낮음	낮음	높음	낮음

CQ8. 코로나19 환자에게 interferon 투여가 표준치료 혹은 무처치 대조군에 비하여 치료효과 및 안전성이 있는가? [RCT]

선행가이드라인 표시	문헌번호	1저자 (출판연도)	연구유형	대상자(N)	중재군(N)	비교/대조군(N)	연구결과	결론	Quality Assessment (ROB)					
									Randomization	allocation concealment	blinding of participants and personnel	blinding of outcome assessment	incomplete outcome data	selective outcome data
ACPG	49	Pan H, WHO SOLIDARITY trial (2020)	open-label RCT	4100 adults hospitalised with moderate to critical COVID-19	three doses of **IFN β-1a** SC over six days + **LPV/r** (2063)	local **standard of care** (2063)	**Death rate ratios: IFN RR=1.16 (0.96-1.39, p=0.11)**. No study drug definitely reduced mortality, initiation of ventilation or hospitalisation duration.	These Remdesivir, HCQ, LPV and IFN regimens appeared to have little or no effect on hospitalized COVID-19, as indicated by overall mortality, initiation of ventilation and duration of hospital stay.	High	Low	Low	Low	Low	Low
ACPG, NIH, IDSA	87	Davoudi-Monfared E.(2020)	open-label RCT	Severe COVID-19(92)	**IFN β-1b SC + the national protocol medications** (42)	**national protocol medications** (LPV/r or ATV/r + HCQ for 7–10 days (39)	**time to the clinical response was not significantly different between the IFN and the control groups** (9.7 ± 5.8 Vs. 8.3 ± 4.9 days, P = 0.95). **On day 14,** 66.7% Vs. 43.6% of patients in the IFN group and the control group, were **discharged (OR= 2.5**; 95% CI, 1.05 - 6.37). **The 28-day overall mortality was significantly lower in the IFN (19%)** than the control group (43.6%),(P = 0.015). E**arly administration significantly reduced mortality (OR=13.5;** 95% CI, 1.5 - 118).	Although IFN did not change the time to reach the clinical response, **adding IFN to the national protocol significantly increased discharge rate on day 14 and decreased 28-day mortality.**	High	Low	Low	Low	Low	Low
NIH	1	Phillip D.M. (2020)	double-blind, placebo-controlled trial	nonventilated patients hospitalized with COVID-19 (1010)	**inhaled IFN β-1a** (once daily for up to 14 days) (50)	**placebo** (n = 48)	**IFN β-1a had greater odds of improvement on the OSCI scale (OR 2·32 [95% CI 1·07–5·04]) on day 15 or 16** and were more likely than those receiving placebo to recover to an OSCI score of 1 (no limitation of activities) during treatment (hazard ratio 2·19 [95% CI 1·03–4·69]).	inhaled IFN β-1a had greater odds of improvement and recovered more rapidly from SARS-CoV-2 infection than patients who received placebo, providing a strong rationale for further trials.	High	Low	High	Low	Low	Low
IDSA	65	Hung IF. (2020)	open-label RCT phase II	Mild to moderate COVID -19 (127)	**LPV/r + ribavirin + IFN β-1b** (86)	**LPV/r only** (40)	**The combination group had a significantly shorter median time from start of study treatment to negative nasopharyngeal swab** (7 days Vs. 12 days; HR 4·37 [95% CI 1·86–10·24]).	**Early triple therapy was superior** to LPV/r alone in **alleviating symptoms and shortening the duration of viral shedding and hospital stay** in patients with mild to moderate COVID-19.	Yes	Low	No	No	No	No

CQ8. 코로나19 환자에게 interferon 투여가 표준치료 혹은 무처치 대조군에 비하여 치료효과 및 안전성이 있는가? [non-RCT]

문헌번호	1저자 (출판연도)	연구유형	대상자(N)	중재군(N)	비교/대조군(N)	연구결과	결론	Quality Assessment (RoBANS)							
								대상자비교 가능성	대상자 선정	교란변수	노출측정	평가자의 눈가림	결과평가	불완전한 결과자료	선택적 결과보고
89	Rodriguez-Garcia, J. L.(2020)	Prosepctive cohort	moderate to severe SARS-CoV-2 pneumonia	LPV/r and HCQ plus either corticosteroids (**CS group**, n=50)	corticosteroids and baricitinib (**BCT-CS group**, n=62)	**A greater improvement in SpO2/FiO2 from hospitalization to discharge in the BCT-CS** Vs. CS group (mean differences 49; 95% CI: 22, 77; P<0.001). A higher proportion of **patients required supplemental oxygen both at discharge** (62.0% vs 25.8%, OR 0.18; 95% CI: 0.08, 0.43) and 1 month later (28.0% vs 12.9%, OR 0.31; 95% CI: 0.11, 0.86) in the CS vs BCT-CS group.	In patients with moderate to severe SARS-CoV-2 pneumonia, **a combination of BCT with CS was associated with greater improvement in pulmonary function** when compared with CS alone.	High	High	Low	Low	Low	High	Low	High
299	Pereda, R (2020)	Prosepctive cohort	confirmed SARS-CoV-2 infection	LPV/r and CQ **with IFN-a2b** IM 3 times per week, for 2 weeks (n=761)	LPV/r and CQ **without IFN-a2b** (n=53)	**The proportion of patients discharged from hospital was higher in the IFN-treated** compared with the non-IFN treated group (95.4% vs. 26.1%, P < 0.01). The case fatality rate for all patients was 2.95%, and for those **patients who received IFN-a2b the CFR was reduced to 0.92.**	**The use of IFN-a2b may contribute to complete recovery of patients.**	Low	Low	High	Low	Low	Low	High	High
623	Wang, N (2020)	Retrospective cohort	confirmed COVID-19 in two regional medical centers (n=446)	**216 early IFN** [IFN + LPV/r (n=83); IFN + UFV (n=94); IFN alone (n=39)] **26 late IFN**;	**204 no IFN** [LPV/r alone (n=122); UFV alone (n=82)]	**early IFN-a2b was associated with reduced in-hospital mortality** in comparison with no IFN-a2b, whereas **late IFN-a2b was associated with increased mortality**. **early IFN-a2b was not associated with hospital discharge or CT scan improvement**, whereas late IFN-a2b was associated with delayed recovery	Administration of **IFN-a2b during the early stage of COVID-19 could induce favorable** clinical responses.	Low	Low	High	Low	Low	Low	Low	High
649	Cao, Y (2020)	single-blind RCT	severe SARS-CoV-2 (n=43)	**ruxolitinib** + standard-of-care treatment (n=22)	**PbO.**+ standard-of-care (n=21)	**Ruxolitinib group was not associated with significantly accelerated clinical improvement.** Ruxolitinib recipients had only a numerically faster clinical improvement. **CT improvement at D14: ruxolitinib group (90%) Vs. control group (61.9%) (p=0.0495)** Levels of 7 cytokines were significantly decreased in the ruxolitinib group	Although **no statistical difference was observed**, ruxolitinib recipients had a numerically faster clinical improvement. **Other favorable outcomes were encouraging to future trials to test efficacy of ruxolitinib**	High	High	Low	Low	Low	High	Low	Low

CQ9. 코로나19 환자에게 회복기 혈장 치료가 표준치료 혹은 무처치 대조군에 비하여 치료효과 및 안전성이 있는가? [RCT]

선행가이드라인 표시	문헌번호	1저자 (출판연도)	연구유형	대상자(N)	중재군(N)	비교/대조군(N)	연구결과	결론	Quality Assessment (ROB)						
									Randomization	allocation concealment	blinding of participants and personnel	blinding of outcome assessment	incomplete outcome data	selective outcome data	
ACPG, IDSA,	127	Li 2020	RCT	103	plasma(52)	standard care(51)	Due to the decreasing incidence of COVID-19 in Wuhan, the trial was terminated early after 103 of the planned 200 patients were enrolled. There was no significant difference between the treatment and control groups in time to clinical improvement within 28 days (HR 1.40; 95% CI, 0.79–2.49; P = 0.26). Among those with severe disease, 91% of the convalescent plasma recipients and 68% of the control patients improved by Day 28 (difference of 23%; OR 1.34; 95% CI, 0. 98–1.83; P = 0.07). Among those with lifethreatening disease, the proportion of patients who showed clinical improvement was similar between the treatment (21%) and control (24%) groups. There was no significant difference in mortality (16% vs. 24% of patients in the treatment and control groups, respectively; P = 0.30). At 24 hours, the rates of negative SARS-CoV-2 viral polymerase chain reaction were significantly higher in the convalescent plasma group (45%) than in the control group (15%; P = 0.003), and differences persisted at 72 hours.	Among patients with severe or life-threatening COVID-19, convalescent plasma therapy added to standard treatment, compared with standard treatment alone, did not result in a statistically significant improvement in time to clinical improvement within 28 days.	low	high	high	low	low	low	
ACPG, NIH	134	Agarwal 2020	RCT	464	plasma(235)	standard care(229)	There was no difference in the primary outcome (time to disease progression and 28-day mortality) across the trial arms. The composite outcome occurred in 44 patients (18.7%) in the convalescent plasma arm and 41 (17.9%) in the control arm. Thirty-four participants (14.5%) in the convalescent plasma arm and 31 patients in the control arm (13.6%) died. In each arm, 17 participants progressed to severe disease (7.2% in the convalescent plasma arm vs. 7.4% in the standard of care arm	no difference	high	low	not blided	not blided			
ACPG	123	Avendano-Sola	RCT	87	plasma(38)	standard care(43)	With 81 patients randomized, there were no patients progressing to mechanical ventilation or death among the 38 patients assigned to receive plasma (0%) versus 6 out of 43 patients (14%) progressing in control arm. Mortality rates were 0% vs 9.3% at days 15 and 29 for the active and control groups, respectively.	Convalescent plasma could be superior to standard of care in avoiding progression to mechanical ventilation or death in hospitalized patients with COVID-19.	high	unclear	unclear	unclear			not peer review
ACPG, IDSA,	128	Gharbharan 202	RCT	86	plasma(43)	standard care(43)	Progression to severe disease or all cause mortality at 28 days after enrolment occurred in 44 (19%) participants in the intervention arm and 41 (18%) in the control arm (risk difference 0.008 (95% confidence interval -0.062 to 0.078); risk ratio 1.04, 95% confidence interval 0.71 to 1.54). No differences in mortality (P = 0.95), length of hospital stay (P = 0.68), or disease severity at Day 15 (P = 0.58) were observed between the study arms	Convalescent plasma was not associated with a reduction in progression to severe covid-19 or all cause mortality.	low	high	high	low	low	low	not peer review

Table 7a. Risk of bias for randomized controlled studies (convalescent plasma vs. no convalescent plasma)

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Li 2020 [1]							
Gharbharan 2020 [2]							

Low | High | Unclear

References

2. Li L, Zhang W, Hu Y, et al. Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients With Severe and Life-threatening COVID-19: A Randomized Clinical Trial. JAMA **2020**.
3. Gharbharan A, Jordans CC, GeurtsvanKessel C, et al. Convalescent Plasma for COVID-19. A randomized clinical trial. MEDRxiv **2020**.

CQ9. 코로나19 환자에게 회복기 혈장 치료가 표준치료 혹은 무처치 대조군에 비하여 치료효과 및 안전성이 있는가? [non-RCT]

선행가이드라인 표시	문헌번호	1저자 (출판연도)	연구유형	대상자(N)	중재군(N)	비교/대조군(N)	연구결과	결론	Quality Assessment (RoBANS)							
									대상자비교가능성	대상자선정	교란변수	노출측정	평가자의 눈가림	결과평가	불완전한 결과자료	선택적 결과보고
IDSA	3	Joyner 2020	1	35322	high titer plasma(515)	low titer (561)	30day mortaloty 22.3% vs. 29.6%, 7 day mortality 8.9% vs. 13.7%	The relationships between reduced mortality and both earlier time to transfusion and higher antibody levels provide signatures of efficacy for convalescent plasma in the treatment of hospitalized COVID-19 patients.	low	low	low	low	low	high	low	low
IDSA, NIH	4	Liu 2020	3	1: 4 mathcing	plasma(39)	standard care(156)	Oxygen requirements on day 14 after transfusion worsened in 17.9% of plasma recipients versus 28.2% of propensity score-matched controls who were hospitalized with COVID-19 (adjusted odds ratio (OR), 0.86; 95% confidence interval (CI), 0.75-0.98; chi-square test P value = 0.025). Survival also improved in plasma recipients (adjusted hazard ratio (HR), 0.34; 95% CI, 0.13-0.89; chi-square test P = 0.027).	Convalescent plasma is potentially effective against COVID-19, but adequately powered, randomized controlled trials are needed.	high	high	low	low	low	high	low	low
IDSA	5	Joyner 2020		20000	ns	ns	The incidence of all serious adverse events was low; these included transfusion reactions (n=78; <1%), thromboembolic or thrombotic events (n=113; <1%), and cardiac events (n=677, ~3%). Notably, the vast majority of the thromboembolic or thrombotic events (n=75) and cardiac events (n=597) were judged to be unrelated to the plasma transfusion per se.	transfusion of convalescent plasma is safe in hospitalized patients with COVID-19	ns	ns	ns	ns	ns	ns	ns	ns
NIH	12	Salazar 2020	3	316	plasma(136)	standard care(251)	The analysis showed a significant reduction (P = 0.047) in mortality within 28 days, specifically in patients transfused within 72 hours of admission with plasma with an anti-spike protein receptor binding domain titer of ≥ 1:1350.	These data suggest that treatment of COVID-19 with high anti-receptor binding domain IgG titer convalescent plasma is efficacious in early-disease patients.	high	high	low	low	low	low	low	low
	319	Abolghasemi 2	1	189	plasma (115)	control (74)	total of 98 (98.2 %) of patients who received convalescent plasma were discharged from hospital which is substantially higher compared to 56 (78.7 %) patients in control group. Length of hospitalization days was significantly lower (9.54 days) in convalescent plasma group compared with that of control group (12.88 days). Only 8 patients (7%) in convalescent plasma group required intubation while that was 20 % in control group.	This clinical study provides strong evidenc	high	high	low	low	low	high	low	low

	223	Rogers 2020	3	241	plasma (64)	control (177)	The incidence of in-hospital mortality was 12.5% and 15.8% in the CP and control groups, respectively (p = 0.52). There was no significant difference in the risk of in-hospital mortality between the two groups (adjusted hazard ratio [aHR] 0.93, 95% confidence interval [CI] 0.39 - 2.20). The overall rate of hospital discharge was not significantly different between the two groups (rate ratio [RR] 1.28, 95% CI 0.91 - 1.81), although there was a significantly increased rate of hospital discharge among patients 65-years-old or greater who received CP (RR 1.86, 95% CI 1.03 - 3.36). There was a greater than expected frequency of transfusion reactions in the CP group (2.8% reaction rate observed per unit transfused)	We did not demonstrate a significant diffe	high	high	low	low	low	high	low	low
	274	Omrani 2020	2	80	plasma (40)	control (40)	The primary endpoint of improvement in respiratory support status within 28 days was achieved in 26 patients (65%) in the SC Group and 31 patients (77.5%) in the CP Group (p = .32). The 28-day all-cause mortality (12.5% vs. 2.5%; p = .22) and viral clearance (65% vs. 55%; p = .49) were not significantly different between the two groups.	In severe COVID-19, convalescent plasma therapy was not associated with clinical benefits	high	high	low	low	low	high	low	low
	103	Rasheed 2020	3	49	plasma (21)	control (28)	Patients who received convalescent plasma showed reduced duration of infection in about 4 days and showed less death rate [1/21 versus 8/28 in control group]	Convalescent plasma therapy is an effectiv	high	high	low	low	low	high	low	low

Table s7b. Risk of bias for non-randomized studies (convalescent plasma vs. no convalescent plasma)

Study + Overall RoB Judgement	Bias due to confounding	Selection Bias	Bias in classification of interventions	Bias due to deviations from interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of reported results
Duan 2020 [1]							
Joyner, Senefeld, et al. 2020 [2]							
Joyner, Wright et al. 2020 [3]							
Liu 2020 [4]							

Low | Moderate | Serious | Critical

CQ10. 코로나19 환자에게 일반적인 정맥용 면역글로불린(Conventional IVIG) 투여가 표준치료 혹은 무처치 대조군에 비하여 치료효과 및 안전성이 있는가? [RCT]

선행가이드라인 표시	문헌번호	1저자(출판연도)	연구유형	대상자(N)	중재군(N)	비교/대조군(N)	연구결과	결론	Quality Assessment (ROB)						
									Randomization	allocation concealment	blinding of participants and personnel	blinding of outcome assessment)	incomplete outcome data	selective outcome data	
ACPG	141	Sakoulas 2020	RCT	33	standard of care (SOC) plus intravenous immunoglobulin (IVIG) 0.5 g/kg/day x 3 days with methylpredniso lone 40 mg 30 minutes (16)	standard care(17)	Seven SOC versus 2 IVIG subjects required mechanical ventilation (p=0.12, Fisher exact test). Among subjects with A-a gradient of >200 mm Hg at enrollment, the IVIG group showed i) a lower rate of progression to requiring mechanical ventilation (2/14 vs 7/12, p=0.038 Fisher exact test), ii) shorter median hospital length of stay (11 vs 19 days, p=0.01 Mann Whitney U), iii) shorter median ICU stay (2.5 vs 12.5 days, p=0.006 Mann Whitey U), and iv) greater improvement in PaO2/FiO2 at 7 days (median [range] change from time of enrollment +131 [+35 to +330] vs +44.5 [-115 to +157], p=0.01, Mann Whitney-U test) than SOC.	This pilot prospective randomized study comprising largely of Latino patients showed that IVIG significantly improved hypoxia and reduced hospital length of stay and progression to mechanical ventilation in COVID-19 patients with A-a gradient >200 mm Hg.	low	unclear	unclear	unclear			not peer review
ACPG		Gharebaghi 2020	RCT	59	IVIG (30): four vials daily for 3 days	placebo (29)	The in-hospital mortality rate was significantly lower in the IVIg group compared to the control group (6 [20.0%] vs. 14 [48.3%], respectively; P = 0.022). Multivariate regression analysis demonstrated that administration of IVIg did indeed have a significant impact on mortality rate (aOR = 0.003 [95% CI: 0.001–0.815]; P = 0.042).	the administration of IVIg in patients with severe COVID-19 infection who did not respond to initial treatment could improve their clinical outcome and significantly reduce mortality rate.	high	unclear	high	unclear			

Table 7a. Risk of bias for randomized controlled studies (convalescent plasma vs. no convalescent plasma)

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Li 2020 [1]							
Gharbharan 2020 [2]							

Low High Unclear

References

2. Li L, Zhang W, Hu Y, et al. Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients With Severe and Life-threatening COVID-19: A Randomized Clinical Trial. JAMA **2020**.
3. Gharbharan A, Jordans CC, GeurtsvanKessel C, et al. Convalescent Plasma for COVID-19. A randomized clinical trial. MEDRxiv **2020**.

CQ10. 코로나19 환자에게 일반적인 정맥용 면역글로불린(Conventional IVIG) 투여가 표준치료 혹은 무처치 대조군에 비하여 치료효과 및 안전성이 있는가? [non-RCT]

선행가이드라인 표시	문헌번호	1저자(출판연도)	연구유형	대상자(N)	중재군(N)	비교/대조군(N)	연구결과	결론	Quality Assessment (RoBANS)							
									대상자비교가능성	대상자선정	교란변수	노출측정	평가자의 눈가림	결과평가	불완전한 결과자료	선택적 결과보고
NIH	1	Shao 2020	cohort	325	IVIG (174)	not IVIG(151)	The study showed no difference in 28-day or 60-day mortality between 174 patients who received IVIG and 151 patients who did not receive IVIG.1 More patients in the IVIG group had severe disease at study entry (71 patients[41%] with critical status in the IVIG group vs. 32 patients [21%] in the non-IVIG group). The median hospital stay was longer in the IVIG group (24 days) than in the non-IVIG group (16 days), and the median duration of disease was also longer (31 days in the IVIG group vs. 23 days in the non-IVIG group). A subgroup analysis that was limited to the critically ill patients suggested a mortality benefit at 28 days, which was no longer significant at 60 days.	The results of this study are difficult to interpret because of important limitations in the study design	high	high	low	low	low	low	low	low

Table s7b. Risk of bias for non-randomized studies (convalescent plasma vs. no convalescent plasma)

Study + Overall RoB Judgement	Bias due to confounding	Selection Bias	Bias in classification of interventions	Bias due to deviations from interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of reported results
Duan 2020 [1]							
Joyner, Senefeld, et al. 2020 [2]							
Joyner, Wright et al. 2020 [3]							
Liu 2020 [4]							

Low | Moderate | Serious | Critical