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Anti-IL-6 receptor antibody treatment for severe COVID-19 and the potential implication of *IL-6* gene polymorphisms in novel coronavirus pneumonia

Tratamiento con anticuerpos anti-receptor de IL-6 para COVID-19 grave y la posible implicación de polimorfismos del gen IL-6 en la nueva neumonía por coronavirus

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Despite the rapid global increase of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, there is currently no effective treatment for patients who have developed severe coronavirus disease 2019 (COVID-19). These severe COVID-19 cases are marked with excess cytokine production and a higher mortality rate. Our previous analysis confirmed that an elevated level of interleukin-6 (IL-6) and C-reactive protein (CRP) are strongly associated with COVID-19 progression.[1,2] Thus, it is reasonable to suggest that the inhibition of IL-6 signaling cascade may effectively treat patients with severe SARS-CoV-2 infection. Another potential consideration regarding disease progression is the role of IL-6 gene polymorphisms. The two most extensively studied *IL-6* gene promoter polymorphisms, −174G/C (rs1800795) and −572C/G (rs1800797), have been shown to affect both the transcription and secretion level of IL-6.[3] Although the role of such polymorphisms have not been studied among COVID-19 patients specifically, it has been demonstrated in other infectious pneumonias.

In this article, we present a systematic review and meta-analysis on the efficacy of anti-IL-6 receptor (anti-IL-6R) antibody in neutralizing IL-6 by evaluating the reduction of the C-reactive protein (CRP) inflammatory marker, clinical outcomes, and the adverse events among severe COVID-19-infected patients. Additionally, a meta-analysis was also performed to estimate the association between *IL-6* gene polymorphism with predisposition as well as disease severity of pneumonia.

All meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[4] Records were identified through electronic databases dated up to May 2020 with search terms such as "COVID-19" "SARS-CoV-2", "IL-6", "anti-IL-6R", "Tocilizumab (TCZ), polymorphism", and "pneumonia" (See Supplementary material). No language restrictions were applied. For TCZ treatment, studies with case-control design evaluating clinical outcomes (*i.e.*, mortality rate, ICU admission, the requirement of mechanical ventilation, and the number of discharged patients) and its adverse events were included. Whereas, for *IL-6* gene polymorphisms, studies were included on the basis of the following criteria: (1) aims to evaluate the association between *IL-6* gene polymorphisms with predisposition to pneumonia; (2) conducted with a case-control design; and (3) evaluates *IL-6* gene polymorphisms in pneumonia patients with or without severe condition (*i.e.*, extra pulmonary bacterial dissemination, sepsis, and multiple organ dysfunction syndrome (MODS)).

Meta-analysis for each gene polymorphism was performed for two or more studies. Genotypic frequency of *IL-6* gene polymorphism was tested for deviation from the Hardy–Weinberg equilibrium (HWE) in the control subjects. The associations between *IL-6* gene polymorphism with predisposition to pneumonia or severity of pneumonia were calculated by pooled odds ratio (OR) and 95% confidence interval (CI). The Z test was used to evaluate the significance of the pooled effect size. Study heterogeneity was evaluated using Q test and I^2 statistic. A significant Q-statistic ($p < 0.10$) indicated heterogeneity across studies, with substantial heterogeneity indicated by an I^2 value over 50%. The

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fixed-effect model (FEM) was used in the absence of heterogeneity, whilst the random-effect model (REM) was implemented if heterogeneity was present. A funnel plot and Begg's test were used to investigate the publication bias if the pooled effect size consisted of 10 or more studies. The value of 0.05 was indicative of the statistical significance. The Newcastle–Ottawa scale (NOS) was used to assess the study quality, in which a score ≥ 7 is considered a good study.[5–10]

Nine case reports/case-series were included for the analysis on anti-IL-6R antibody treatment (summarized in Table 1) with a total sample of $n = 66$ patients. A large proportion of the samples (89%) were male, with ages ranging from 42 to 73 years old.[10–18] All patients developed severe COVID-19, marked by acute respiratory distress syndrome (ARDS) during admission, and more than half of studies reported the use of mechanical ventilators. Hypertension was the most common co-morbidity observed in patients with SARS-CoV-2 infection, followed by diabetes mellitus (DM), cerebrovascular disease, cardiovascular disease (CVD), and chronic kidney disease (CKD). Eight of the studies administered TCZ treatment,[11–18] while one utilized Siltuximab.[19] One to three times injection of anti-IL-6R antibody was mainly given during the onset of ARDS,[11,13–15,18] while the rest were administered several days after the admission/ARDS onset[12,15,18,19] or depending on the level of IL-6 or CRP.[17] Several additional treatments were given in

Table 1
Systematic review of case report and case-series evaluating anti-IL-6R treatment in severe COVID-19.

Characteristics	Michot et al.	Zhang et al.	De Luna et al.	Cellina et al.	Di Giambenedetto et al.	Radbel et al.	Gritti et al.	Xu et al.	Luo et al.
Location	France	China	France	Italy	Italy	USA	Italy	China	China
Study type	Case report	Case report	Case report	Case report	Case report	Case report	Retrospective case-series	Retrospective case-series	Retrospective case-series
Number of cases	1	1	1	1	3	2	21	21	15
Age [years]	42	60	45	64	56.33 [mean]	54.5 [mean]	64 [median]	56.8 [mean]	73 [median]
Males, %	100	100	100	100	100	50	85.7	85.7	80
Major clinical feature	ARDS	ARDS	ARDS	ARDS	ARDS	ARDS	ARDS	ARDS	ARDS
Onset of ARDS	7-days after admission/2-days after SARS-CoV-2 was confirmed	15-days after admission/12-days after SARS-CoV-2 was confirmed	1 day after admission	5-days after admission	8-days after admission (patient 1) At admission (patient 2) 2-Days after admission (patient 3)	2-days after admission	NR	NR	6-days after the onset of fever
Mechanical ventilation	No	NR	No	Yes	Yes	Yes	Yes	NR	Yes (15%)
Co-morbidities	Renal cell carcinoma	Multiple myeloma	SCD	NR	Hypertension	DM, rheumatoid arthritis, aplastic anemia	Hypertension, CVD, CKD, DM malignancies, cerebrovascular disease	Hypertension, DM, CHD, COPD, CKD, Brain infarction, Bronchiectasis, Auricular fibrillation	Hypertension, DM, stroke
Anti-IL-6R	TCZ	TCZ	TCZ	TCZ	TCZ	TCZ	Siltuximab	TCZ	TCZ
Time to start Anti-IL-6R treatment	At the onset of ARDS	24-days after admission/9-days after the onset of ARDS	At the onset of ARDS	At the onset of ARDS	At the onset of ARDS (patient 1 and 3) 4-Days after admission (patient 2)	2-days after diagnosed with ARDS/at the onset of septic shock (patient 1) At the onset of ARDS and septic shock (patient 2)	3-Days after admission [median]	NR	Depending on the level of IL-6 or CRP
Dose	8 mg/kg IV (2 times, 8 h interval)	8 mg/kg IV (1 time)	8 mg/kg IV (1 time)	8 mg/kg IV (2 times, 12 h interval)	8 mg/kg IV (2 or 3 times, 12 h interval for the second dose or 24/36 h for the third dose)	400 mg IV (1 time, patient 1) 560 mg IV and 700 mg IV (2 times, 2 days interval, patient 2)	11 mg/kg IV (1 time)	400 mg IV (1 time)	80–600 mg IV (≥2 times)
Characteristics	Michot et al.	Zhang et al.	De Luna et al.	Cellina et al.	Di Giambenedetto et al.	Radbel et al.	Gritti et al.	Xu et al.	Luo et al.
Co-treatment	Ceftriaxone, Piperacilline tazobactam, Lopinavir/ Ritonavir	Moxifloxacin Umifenovir	Amoxicillin-clavulanic acid HCQ	NR	Lopinavir/ Ritonavir HCQ	HCQ, azithromycin,NE (vasopressor), steroids	NR	Lopinavir, Methyl-prednisolone	Methyl-prednisolone

Table 1 (*Continued*)

Evaluation time (for CRP level)	Day-4 post-treatment	Day-7/14 post-treatment	NR	Day-1 post-treatment	Day-2/3/10 post-treatment	Day-1/2/3 post-treatment	Day-5 post-treatment	Day-1/3/5 post-treatment	Day-1/2/3/4/5/6/7 post-treatment
% Reduction of CRP from baseline (before treatment)	85.33	10/77.9	NR	71.42	77.29/95.72/98	-10.16/12.46/66.23	~78.63	49.20/85.86/96.37	64.89/73.93/86.65/92.83/82.42/58.75/88.64
IL-6 level	NR	82.88% reduction after 10-days of TCZ treatment	NR	NR	NR	–	NR	IL-6 level tended to spike and then decreased following TCZ treatment	NR
Chest CT	Improvement after 4-days TCZ treatment	Improvement after 12-days TCZ treatment	NR	Improvement after 7-days TCZ treatment	Improvement after 2 or 3-days TCZ treatment	NR	NR	NR	Improvement after TCZ treatment
Clinical outcome	Generally improved (afebrile and decreased oxygen consumption	Gradually recovered after TCZ treatment	Generally improved after 1-day TCZ treatment	Generally improved (released from mechanical ventilation)	Generally improved (afebrile and improvement of PaO_2-to-FiO_2 ratio)	Died (both patients progressed to secondary hemophagocytic lymphohistiocytosis (sHLH).	33% of patients were clinically improved (released from mechanical ventilation)	Generally improved	Generally improved (afebrile and improvement of the peripheral oxygen saturation)

ARDS, acute respiratory distress syndrome; CVD, cardiovascular disease; CKD, chronic kidney disease; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; DM, diabetes mellitus; HCQ, hydroxychloroquine; IV, intravenous; NR, not reported; SCD, sickle cell disease. TCZ, Tocilizumab.

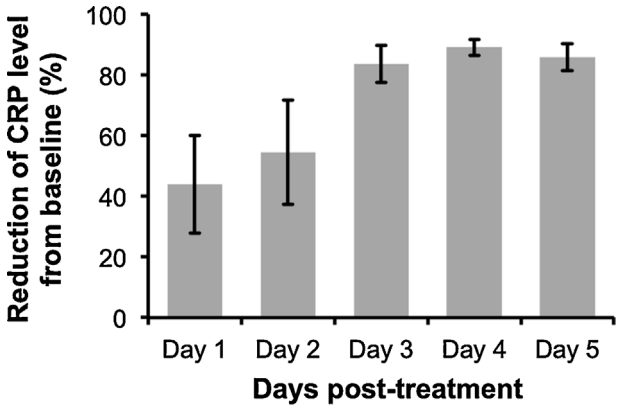

Fig. 1. Pooled reduction of C-Reactive Protein following administration of anti-IL-6R antibody in severe pneumonia. Figure shows mean ± standard error of the mean. $n = 2–4$ studies per group.

the studies, including antivirals, antibiotics, corticosteroids, antimalaria (hydroxychloroquine/HCQ), and vasopressors.

The analysis revealed that despite some variability in the levels of CRP post-treatment with anti-IL-6R antibody, peak CRP reduction was observable at 3 to 4-days after the administration (Fig. 1). Additionally, anti-IL-6R antibody treatment also resulted in the suppression of IL-6 levels[12,16] and remarkable reduction of COVID-19 severity characterized by the improvement of chest CT and its symptoms. However, as reported by Radbel et al.,[18] adverse secondary hemophagocytic lymphohistiocytosis (sHLH) occurred despite the lowered CRP levels, indicating the potential risk of side effects with this treatment. Thus, further studies evaluating efficacy and safety of anti-IL-6R antibody in treating COVID-19-infected patients is indispensable.

Five case-control studies evaluating TCZ treatment in severe COVID-19 were initially included[20–24]; followed by the exclusion of one study in which the control group displayed milder clinical presentation[24] (Table 2). No statistical significance was observed between the pooled mortality rates of the TCZ and standard treatment (STD) groups, which may be due to the heterogeneity between studies. However, it can be noted that relative to STD treatment, TCZ treatment was marginally associated with lower mortality rate (HR = 0.39, 95%CI 0.01–0.77, $p = 0.09$, Fig. 2A; OR = 0.30, 95%CI 0.08–1.10, $p = 0.07$, Fig. 2B). In a study conducted by Sciascia et al.,[25] TCZ treatment was shown to increase the likelihood of survival among severe COVID-19 patients (Table 2).

This analysis also showed that invasive mechanical ventilation (IMV) was required less in the TCZ group (OR = 0.10, 95%CI 0.01–0.77, $p = 0.03$, Fig. 2C). No statistical difference was observed in terms of ICU admissions, the number of discharged patients, and the adverse effects of treatment (bacteremia and an elevated level of AST/ALT) between the two groups (Fig. 2D, E, Supplemental Fig. 1, respectively). Interestingly, however, Morena et al.[26] demonstrated that 67% of patients administered with TCZ showed an improvement in their clinical severity class. Thus, the administration of TCZ seems beneficial in lowering the mortality rate and increased favorable clinical outcomes in patients with severe SARS-CoV-2 infection. However, additional data are still required to understand the effect of TCZ in treating patients with severe and critically ill COVID-19.

For the analysis on *IL-6* gene polymorphisms and pneumonia, 24 articles were found using the aforementioned search strategy. Irrelevant articles were subsequently excluded, leaving a total of 11 eligible studies. The total sample included for analysis were 3958 cases and 3671 controls; 717 cases and 579 controls for *IL-6* –174G/C and –572C/G polymorphisms, respectively[27–30] (Supp. Refs. 1–7). To assess the association between *IL-6* –174G/C with pneumonia severity, 671 severe and 2910 non-severe cases were examined[29] (Supp. Ref. 3,6]) The characteristics of the included studies are shown in Table 2. All but four of the studies[30] (Supp. Ref. 2,3,5) did not comply with the HWE ($p < 0.05$). Overall, a lack of association between *IL-6* –174G/C and –572C/G polymor-

Table 2
Characteristic of retrospective case-control and prospective cohort studies included in the analysis of anti-IL-6R treatment in severe COVID-19.

Author	Location	No. of TCZ/STD treated patients	TCZ eligibility criteria	Therapy	Outcome at days	Survival rate (HR, 95% CI)	Mortality		Required IMV		ICU admission		Discharge		Adverse effect*	
							TCZ	STD	TCZ	STD	TCZ	STD	TCZ	STD	TCZ	STD
Campochiaro et al.	Italy	32/33	2x Positive RT-PCR of SARS-CoV-2 on nasopharyngeal swab; hyper-inflammation (CRP, ≥100 mg/L or r ferritin ≥ 900 ng/mL); severe respiratory involvement (chest X-ray/CT, $SaO_2 \leq 92\%$, PaO_2:$FiO_2 \leq 300$ mmHg)	STD: HCQ, lopinavir/ritonavir, ceftriaxone, azithromycin, anti-coagulation prophylaxis TCZ: STD + TCZ 400 mg IV (1 time, 24 h interval for the second dose)	28	HR for death 0.44, 95% CI 0.167–1.184, $p = 0.122$	5/32	11/33	0/32	1/33	–	–	20/32	16/33	4/32[a] 5/32[b]	4/33 6/33
Capra et al.	Italy	62/23	Confirmed SARS-CoV-2, and one of the following criteria: RR ≥ 30 breaths/min, $SpO_2 \leq 93\%$, $PaO_2/FiO_2 \leq 300$ mmHg, severe respiratory involvement by chest X-ray	STD: HCQ, lopinavir, ritonavir TCZ: STD + TCZ 400 mg IV or 324 mg SC (1 time)	35	HR for death 0.035, 95% CI 0.004–0.347, $p = 0.004$	2/62	11/23	–	–	–	–	23/62	8/23	–	–
Colaneri et al.	Italy	21/91	Confirmed SARS-CoV-2, CRP > 5 mg/dl, PCT < 0.5 ng/mL, PaO_2:$FiO_2 < 300$; ALT < 500 U/L	STD: HCQ, azithromycin, prophylactic dose of low weight heparin, and methylprednisolone TCZ: STD + TCZ 400 mg IV	7	–	5/21	19/91	–	–	3/21	12/91	–	–	0/21[b]	0/91
Klopfensteina et al.	France	20/25	Confirmed SARS-CoV-2; failure of standard treatment, oxygen therapy ≥ 5 l/min, >25% of lung damages on chest computed tomography (CT) scan, and ≥ 2 parameters of inflammation (high level of ferritin, CRP, D-dimers, lymphopenia, and LDH)	STD: HCQ, lopinavir-ritonavir, antibiotics, corticosteroids TCZ: STD + TCZ (1 or 2 doses)	11	–	5/20	12/25	0/20	8/25	0/20	11/25	11/20	11/25	–	–

Table 2 (*Continued*)

Author	Location	No. of TCZ/STD treated patients	TCZ eligibility criteria	Therapy	Outcome at days	Survival rate (HR, 95% CI)	Mortality		Required IMV		ICU admission		Discharge		Adverse effect*	
							TCZ	STD	TCZ	STD	TCZ	STD	TCZ	STD	TCZ	STD
Quartuccio et al.	Italy	42/69	Confirmed SARS-CoV-2; level of CRP and IL-6	STD: antivirals, antimalarials, glucocorticoids, antibiotics, LMWH TCZ: STD + TCZ 8 mg/kg IV single infusion	12	–	4/42	0/69**	–	–	–	–	–	–	–	–

Author	Location	No. of patients	TCZ eligibility criteria	Therapy	Outcome (HR, 95% CI)		
					Adverse effect	Clinical improvement	Survival rate
Morena et al.	Italy	51	Confirmed SARS-CoV-2, age ≥ 18 years, RR ≥ 30 min^{-1}, SpO_2 < 93%, PaO_2/FiO_2 < 250 mmHg, IL-6 plasma level > 40 pg/mL.	TCZ 400 mg IV or 8 mg/kg (1 time, 12 h interval for the second dose)	Increased AST/ALT (29%), Bacteremia (27%)	HR 67% (95% CI 56–68) Clinical improvement based on severity or discharge, 30 days follow up	Mortality rate 27%, 30 days follow up
Sciascia et al.	Italy	56	Confirmed SARS-CoV-2, SpO_2 < 93%, PaO_2/FiO_2 < 300 mmHg, CRP or D-dimer > 10× normal values, LDH > 2× the upper limits, ferritin > 1000 ng/mL	TCZ 8 mg/kg IV or 324 mg SC (1 or 2 doses)	No adverse effect was reported	–	TCZ increased survival rate, HR 2.2 (95% CI 1.3–6.7), $p < 0.05$, Survival rate according to D-dimer levels, 14 days follow up

TCZ, Tocilizumab; STD, Standard treatment; *adverse effects including secondary infection[a] or severe hepatic injury/increase ALT/AST[b]; **milder clinical presentation; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; CT, computerized tomography; FiO_2, fraction of inspired oxygen (FiO_2); HCQ, hydroxychloroquine; ICU, intensive care unit; IV, intravenous; IMV, invasive mechanical ventilation; LDH lactate dehydrogenase; PaO_2, partial pressure of oxygen; PCT, procalcitonin; RT-PCR, reverse transcription polymerase chain reaction; SC, subcutaneous, SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

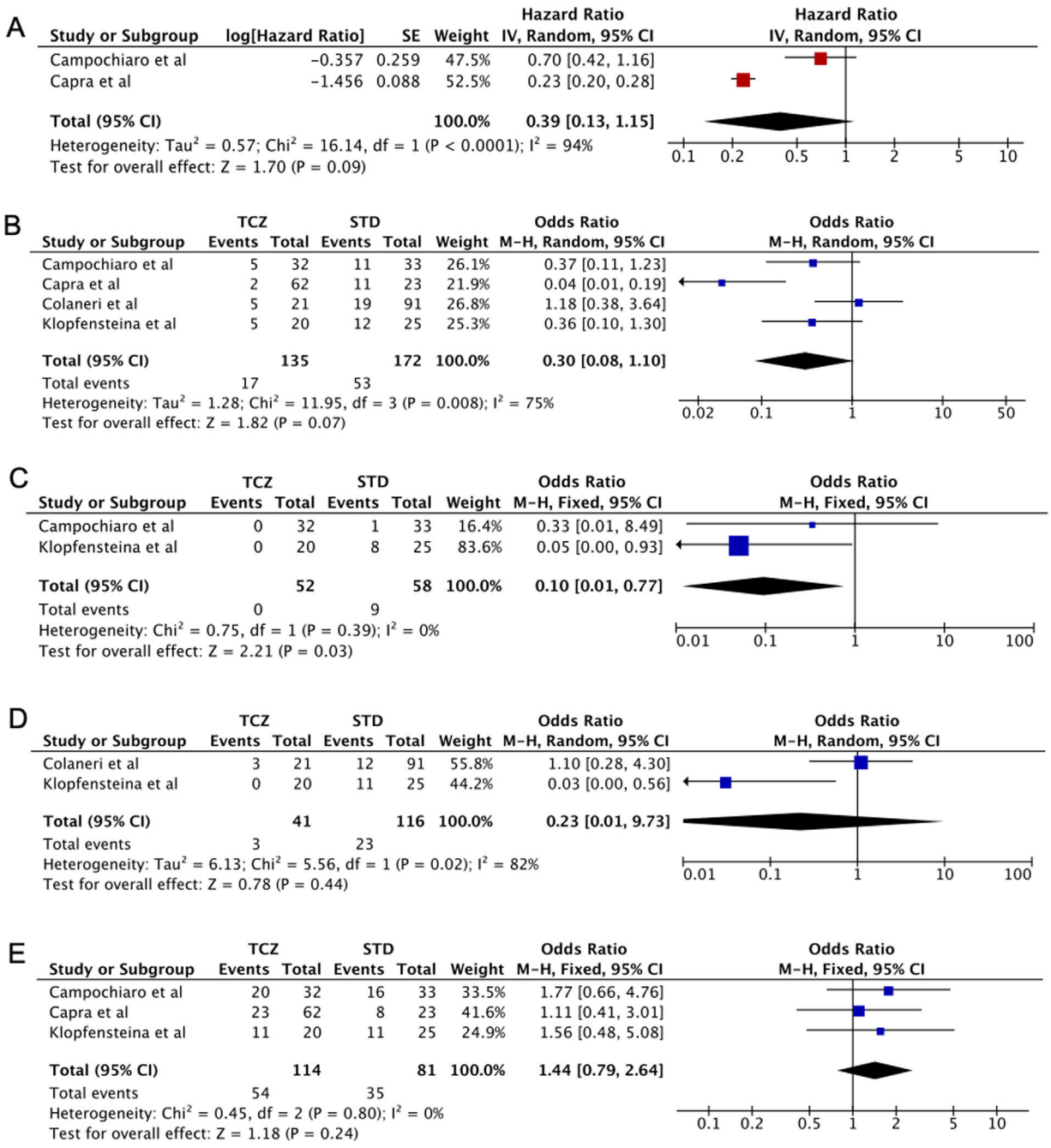

Fig. 2. (A) Forest plot of studies reporting hazard ratio (HR) that investigates the mortality rate between Tocilizumab (TCZ) group and standard treatment (STD) group. (B–E) Forest plot of pooled studies evaluating mortality rate, invasive mechanical ventilation (IMV) requirement, ICU admissions, and the number of discharged patients between Tocilizumab (TCZ) group and standard treatment (STD) group, respectively.

phisms with pneumonia predisposition was observed in all genetic models (Table 3). Additionally, results remained insignificant following subgroup analysis based on ethnicity and age (data not shown).

Interestingly however, we found that *IL-6* −174G/C polymorphism was significantly associated with the severity of pneumonia (C vs. G, OR: 1.33, 95%CI 1.04–1.69, $p = 0.019$, Fig. 3A; particularly in the Caucasian population, OR: 1.15, 95%CI 1.00–1.33, $p = 0.049$; CC+GC vs. GG; OR: 1.20, 95%CI 1.07–1.53, $p = 0.006$, Fig. 3B; CC vs. GG; OR: 1.55, 95%CI 1.18–2.03, $p = 0.001$, Fig. 3C, Table 3). In line with our results, Feng et al. [Supp. Ref. 8] observed that carriers of the *IL-6* −174G/C had a 2.42-fold higher risk for pneumonia-induced septic shock, thereby implying a higher tendency of severe pneumonia in patients harboring the *IL-6* −174C. Indeed, the CC genotype has been correlated with significantly higher IL-6 levels [Supp. Ref. 3,9]. Moreover, it has been shown that the haplotype spanning from −1363 to +4835 from the transcription start site of *IL-6* conferred susceptibility to acute lung injury (ALI) [Supp. Ref. 10] (Table 4).

Tocilizumab, Sarilumab, or Siltuximab are humanized recombinant monoclonal antibodies that inhibit IL-6 signal transduction of IL-6 by binding with the soluble and membrane IL-6R, sIL-6R and mIL-6R, respectively. So far, anti-IL-6R antibody is mainly used to treat rheumatoid arthritis patients with favorable safety profile.[11] Since these agents are immunosuppressive, their administrations are normally contraindicated in patients with active

Table 3
The characteristics of included studies on IL-6 gene polymorphism and pneumonia.

First author, Year	Age group	Country	Ethnicity	Sample size (cases/controls)	Genotype (wtwt/wtmt/mtmt)		*p* value for HWE	NOS score
					Cases	Controls		
−174G/C [rs1800795]								
Endeman, 2011	Adult	The Netherlands	Caucasian	200/311	83/92/25	113/150/48	0.878	8
Mao, 2016	Adult	China	Asian	162/200	68/46/48	97/66/37	**0.000**	8
Martinez-Ocana, 2013	Adult	Mexico	Caucasian	65/46	53/12/0	39/7/0	0.576	8
Martın-Loeches, 2012	Adult	Spain	Caucasian	953/1246	581/516/130	438/413/102	0.752	8
Salnikova, 2013 [a]	Adult	Russia	Caucasian	334/141	37/80/22	103/150/69	0.299	8
Salnikova, 2013 [b]	Adult	Russia	Caucasian	216/105	32/56/12	83/81/42	**0.009**	8
Schaaf, 2005	Adult	Germany	Caucasian	100/50	29/51/20	17/25/8	0.812	8
Sole-Violan, 2010	Adult	Spain	Caucasian	1413/1162	533/485/120	590/502/123	0.288	8
Zhao, 2017	Pediatric	China	Asian	415/300	391/24/0	296/4/0	0.907	8
Zidan, 2014	Pediatric	Egypt	African	100/110	32/55/13	22/60/28	0.323	8
−572C/G [rs1800797]								
Chou, 2016	Adult	Taiwan	Asian	279/156	184/62/33	106/32/18	0.000	8
Su, 2019	Pediatric	China	Asian	438/423	206/193/39	351/58/14	0.000	8
First Author, Year	Age group	Country	Ethnicity	Sample Size (Severe/Non-severe)	Genotype (GG/GC/CC)		*p* value for HWE	NOS score
					Severe	Non-severe		
−174 G/C [rs1800795]								
Mao, 2016	Adult	China	Asian	188/200	56/37/95	68/46/48	**0.000**	8
Schaaf, 2005	Adult	Germany	Caucasian	25/75	3/15/7	26/36/13	0.929	8
Sole-Violan, 2010 [a]	Adult	Spain	Caucasian	159/817	73/68/18	392/341/84	0.441	8
Sole-Violan, 2010 [b]	Adult	Spain	Caucasian	162/817	68/76/18	392/341/84	0.441	8
Sole-Violan, 2010 [c]	Adult	Spain	Caucasian	137/1001	59/62/16	474/423/104	0.504	8

Bold values indicate the results were deviated from HWE (Hardy–Weinberg equilibrium); mt, mutant type; wt, wild type.

Table 4
Meta-analysis results of IL-6 gene polymorphism and pneumonia.

Genetic model	Group	No. of studies	Test of association				Test of heterogeneity		*p* Egger's test
			OR	95% CI	*p*	Model	*p* (*Q* test)	I^2 (%)	
A. Case - Control									
−174G/C [rs1800795]									
C vs. G	Overall	10	1.02	[0.88; 1.18]	0.776	Random	0.006	60.71	0.477
	Overall*	8	1.02	[0.94; 1.10]	0.591	Fixed	0.260	21.23	0.502
CC vs. GC+GG	Overall	8	0.92	[0.69; 1.18]	0.462	Random	0.015	59.41	0.443
	Overall*	7	0.97	[0.75; 1.24]	0.833	Random	0.051	51.99	0.694
CC+GC vs. GG	Overall	10	1.08	[0.90; 1.30]	0.394	Random	0.025	52.56	0.304
	Overall*	8	1.04	[0.94; 1.15]	0.432	Fixed	0.400	3.84	0.211
CC vs. GG	Overall	8	0.94	[0.72; 1.24]	0.690	Random	0.033	53.86	0.514
	Overall*	7	1.03	[0.87; 1.21]	0.711	Fixed	0.226	26.52	0.949
GC vs. GG	Overall	10	1.10	[0.91; 1.33]	0.312	Random	0.028	51.82	0.229
	Overall*	8	1.04	[0.93; 1.16]	0.447	Fixed	0.243	23.34	0.252
−572C/G [rs1800797]									
G vs. C	Overall	2	2.06	[0.57; 7.45]	0.268	Random	0.000	97.25	NA
GG vs. CG+CC	Overall	2	1.70	[0.62; 4.65]	0.293	Random	0.022	80.90	NA
GG+CG vs. CC	Overall	2	2.46	[0.50; 11.97]	0.262	Random	0.000	97.26	NA
GG vs. CC	Overall	2	2.23	[0.51; 9.75]	0.284	Random	0.000	90.90	NA
CG vs. CC	Overall	2	2.54	[0.51; 12.49]	0.251	Random	0.000	96.50	NA
B. Severe - Non-severe									
−174 G/C [rs1800795]									
C vs. G	Overall	5	**1.33**	**[1.04; 1.69]**	**0.019**	Random	0.015	67.44	0.320
	Caucasian	4	**1.15**	**[1.00; 1.33]**	**0.049**	Fixed	0.409	0	0.043
CC vs. GC+GG	Overall	5	1.42	[0.98; 2.06]	0.058	Random	0.088	50.60	0.743
	Caucasian	4	1.16	[0.85; 1.57]	0.331	Fixed	0.842	0	0.002
CC+GC vs. GG	Overall	5	**1.20**	**[1.07; 1.53]**	**0.006**	Fixed	0.240	27.16	0.059
	Caucasian	4	1.21	[0.99; 1.47]	0.054	Fixed	0.308	16.64	0.061
CC vs. GG	Overall	5	**1.55**	**[1.18; 2.03]**	**0.001**	Fixed	0.121	45.15	0.561
	Caucasian	4	1.28	[0.92; 1.77]	0.131	Fixed	0.392	0	0.004
GC vs. GG	Overall	5	1.17	[0.96; 1.43]	0.103	Fixed	0.460	0	0.229
	Caucasian	4	1.20	[0.98; 1.48]	0.076	Fixed	0.371	4.21	0.086

Bold values indicate statistically significant differences between severe and non-severe cases. Asterisk (*) indicates that studies deviated from HWE (Hardy–Weinberg equilibrium) were excluded.

infection, thrombocytopenia, and an elevated liver function, which is also observed in COVID-19-infected patients[2] (Supp. Ref. 11). Interestingly, however, pooled results collected from nine studies indicated that anti-IL-6R antibody treatment could effectively treat severe COVID-19-infected patients, marked by suppression of CRP and improvement of clinical symptoms. This may be due to transcriptional induction of the *CRP* gene was inhibited by TCZ, which then further suppressed inflammatory responses during SARS-

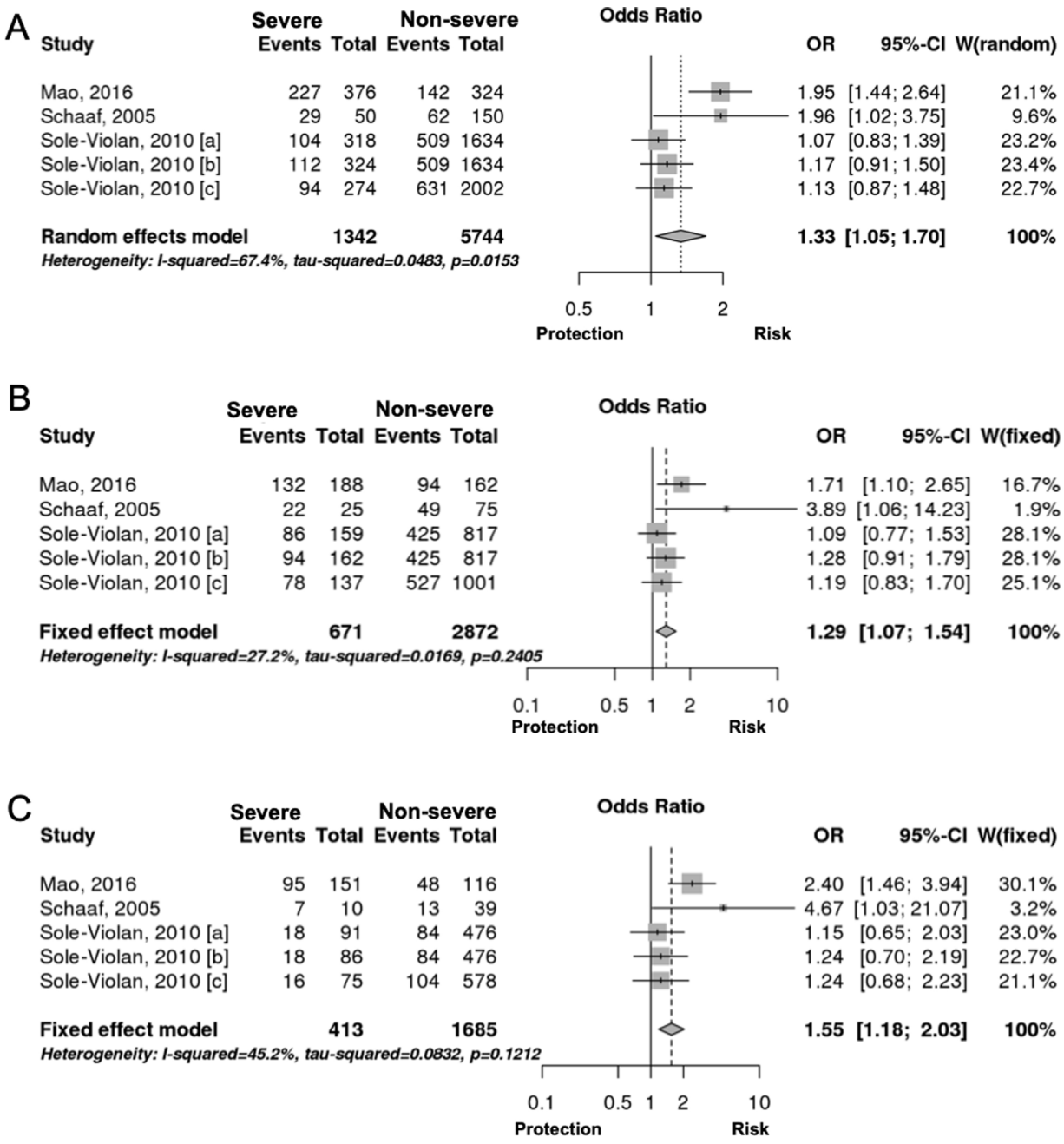

Fig. 3. Association between *IL-6* −174G/C polymorphism with the severity of pneumonia. (A) C vs. G; (B) CC+GC vs. GG; (C) CC vs. GG.

CoV-2 infection. Although *IL-6* gene polymorphism results may not directly correlate with novel coronavirus pneumonia (NCP), this analysis demonstrated that *IL-6* −174C allele carrier status is associated with higher level of IL-6 production and more severe forms of pneumonia in general. This analysis strengthens the notion that IL-6 plays a pivotal role in novel coronavirus pneumonia (NCP) progression.

At present, 32 clinical trials have been registered (clinicaltrials.gov) to evaluate the efficacy and safety of anti-IL-6R antibodies. Despite the limited number of participants so far, suppression of IL-6 signaling cascade shows a promising therapy in the ARDS induced by SARS-CoV-2 infection.

Conflict of interest

None to declare.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.medcli.2020.07.002.

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