Review

Mortality in tocilizumab-treated patients with COVID-19: a systematic review and meta-analysis

O. Berardicurti[1], P. Ruscitti[1], F. Ursini[2,3], S. D'Andrea[4], J. Ciaffi[2], R. Meliconi[2,3], A. Iagnocco[5], P. Cipriani[1], R. Giacomelli[6]

[1]Department of Biotechnological and Applied Clinical Sciences, Rheumatology Unit, University of L'Aquila, L'Aquila Italy;
[2]IRRCS Istituto Ortopedico Rizzoli, Bologna, Italy;
[3]Department of Biomedical and Neuromotor Sciences, University of Bologna;
[4]Department of Life, Health and Environment Sciences, Andrology Unit, University of L'Aquila, L'Aquila Italy;
[5]Dipartimento Scienze Cliniche e Biologiche, Università degli Studi di Torino, Italy;
[6]Allergology, Immunology, Rheumatology Unit, Department of Medicine, Università Campus Bio-Medico di Roma, Italy.

Onorina Berardicurti, MD
Piero Ruscitti, MD, PhD
Francesco Ursini, MD, PhD
Settimio D'Andrea, MD
Jacopo Ciaffi, MD
Riccardo Meliconi, MD
Annamaria Iagnocco, MD
Paola Cipriani, MD, PhD
Roberto Giacomelli, MD, PhD

Please address correspondence to:
Onorina Berardicurti,
Reumatologia,Dipartimento di Scienze Cliniche Applicate e Biotecnologiche,
Edificio Delta 6,
Università dell'Aquila,
Via dell'Ospedale,
67100 L'Aquila, Italy.
E-mail: berardicurtio@libero.it
onorina.berardicurti@graduate.univaq.it

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ABSTRACT

Objective. *People who are exposed to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) could develop a potentially fatal disease with lung involvement and severe cytokine storm syndrome (CSS) – coronavirus disease 2019 (hereafter, COVID-19). Tocilizumab (TCZ) was administered to these subjects, despite the lack of randomised clinical trial data. Hence, summarising data on the mortality rate and related risks factors may help physicians to correctly administer TCZ.*

Methods. *We performed a systematic review and meta-analysis on mortality rate in TCZ- treated patients with COVID-19 according to the PRISMA guidelines. The pooled mortality rate in TCZ-treated persons was calculated and meta-regressions were done to investigate associated factors.*

Results. *We included 22 studies and 1520 TCZ-treated patients (mean age: 61 years, 95% CI: 59–64; male: 71%, 95% CI: 64–78%). The mortality estimated pooled prevalence was 19% (95% CI: 13–25, I2=100%, p<0.00001) and improvement estimated pooled prevalence was 71% (95% CI: 62–81). Factors associated with the mortality are the number of patients in intensive care unit, the number of patients requiring invasive ventilation and the sera C-reactive protein value before TCZ administration. We observed a reduction in the odds of mortality in TCZ-treated patients when compared to those treated with other therapies (OR=0.47, 95% CI: 0.22–0.98, p=0.004).*

Conclusion. *This study showed that the mortality pooled prevalence in TCZ-treated patients is lower than the overall mortality reported in patients with severe COVID-19.*

Introduction

On March 11, 2020, the World Health Organization (WHO) declared the massive global outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) to be a pandemic. Understandably, we are facing one of the most important health challenges in the 21st century. In this context, evidence-based medicine (EBM) data are crucial to correctly allocate our resources to optimise COVID-19 management. Although the majority of infected patients show only a flu-like illness, characterised by high fever, cough, myalgia, and fatigue, lung involvement has been reported in 70% cases (1). In those with pulmonary involvement, the associated negative prognostic factors are age; male sex; co-morbidities such as cardiovascular diseases (CVDs); co-infections; and increased serum levels of pro-inflammatory markers such as C-reactive protein (CRP), interleukin (IL)-6, and ferritin (2). IL-6 is an inflammatory molecule involved in the development of cytokine storm syndrome (CSS), which characterises severe COVID-19 (3-5). Inhibiting IL-6 is considered one of the best therapeutic options during CSS, as previously reported in chimeric antigen receptor T-cell therapy in oncologic patients (6). Tocilizumab (TCZ) is a recombinant humanised antibody directed against the IL-6 receptor, and it is capable of inhibiting the binding with both soluble and cell-surface receptors, thereby preventing the downstream signaling cascade (7).

Accordingly, the first clinical trial was planned in China to investigate the efficacy and safety of TCZ for prompt improvement of respiratory function and the overall clinical scenario in Chinese patients with severe COVID-19 (ChiC-

TR2000029765). This study confirmed the positive results already reported in some case reports (8-10). After these data, TCZ has been widely administered, despite the lack of high-quality studies and randomised clinical trials. Furthermore, because of the clinical heterogeneity of symptoms in SARS-CoV-2 infected patients, it is imperative an early identification of a likely sub-group of patients who might benefit from TCZ treatment. Keeping in mind these critical points and being the pandemic still active, over-stressing healthcare systems world-wide, a systematic analysis of the growing body of literature may be of interest to provide an EBM information concerning this potential very important treatment strategy.

Therefore, we conducted a systematic literature review and meta-analysis of observational studies to determine the outcome of COVID-19 in TCZ-treated patients in terms of mortality rate and related risk factors, as well as to summarise the clinical and serological characteristics of TCZ-treated COVID-19 patients.

Materials and methods

Protocol

This study was conducted according to the Cochrane Collaboration and the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement (11). The PRISMA checklist is presented in Supplementary Table S1.

Eligibility criteria

In this study, we included all peer-reviewed published articles that reported demographic, clinical, and serological characteristics of TCZ-treated patients with SARS-CoV2 infection. We selected all the studies conducted in COVID-19 patients with a confirmed diagnosis (Population) and treated vs. non-treated with TCZ (Intervention and Control) that reported the mortality rate and associated factors (Outcome). We included all the studies published from January 1, 2020 to July 21, 2020. Review articles, case reports, opinion articles, letters, brief reports, non-English publications, and those with missing data were excluded.

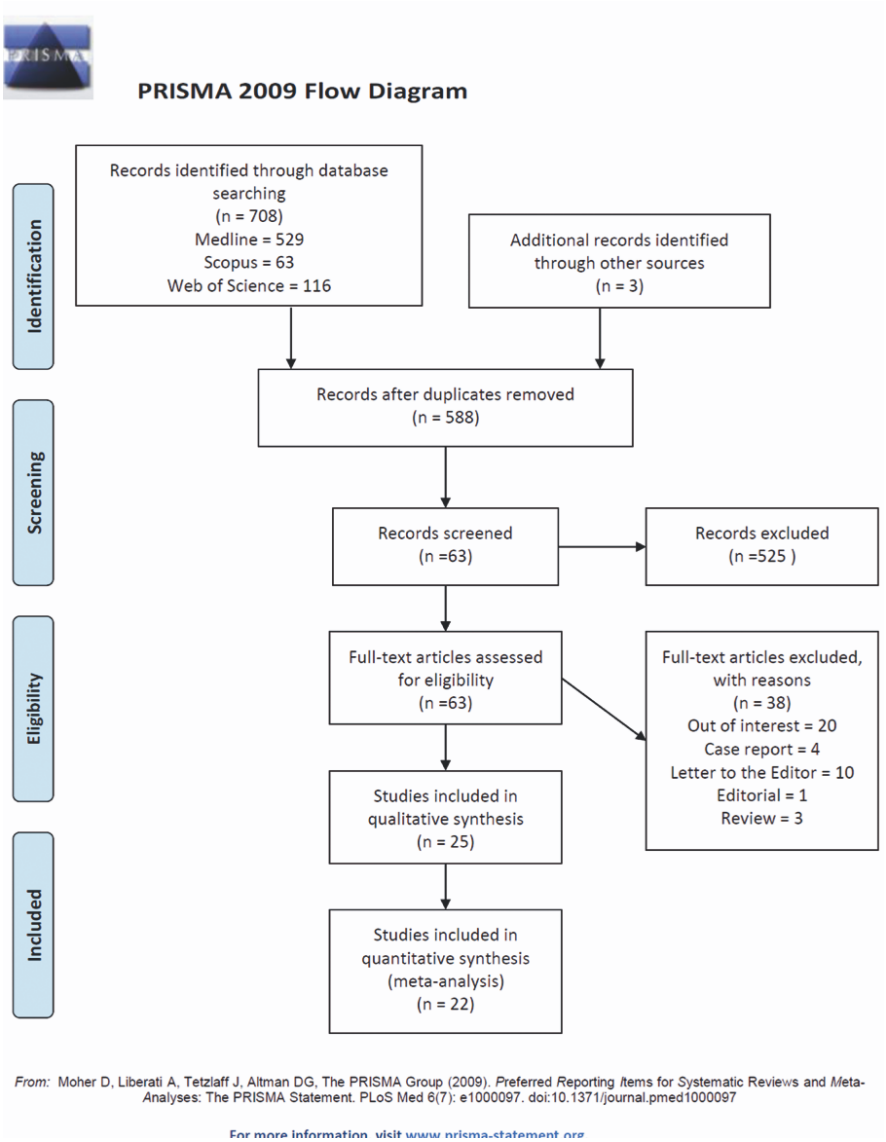


Fig. 1. PRISMA 2009 flow diagram.

Search strategy and study selection

We conducted a systematic search in MEDLINE, Cochrane Library, SCOPUS, and Web of Science databases to identify all relevant English-language publications, with the terms: ("SARS-CoV2" OR "COVID-19") AND ("tocilizumab" OR "il6" OR "anti-IL6"). Two independent reviewers (OB and PR) first screened the retrieved papers based on the title and abstract (Fig. 1). If it was not clear from the title and abstract whether the paper contained relevant data, the full paper was retrieved. The list of all excluded papers after full-text assessment is reported in Supplementary Table S2. Finally, we scrutinised the reference lists of the identified articles to find additional pertinent studies.

Data extraction

Data from the selected articles were extracted according to the first author; publication year; country or region; age of participants; study type; number of participants; number of patients treated with TCZ; sex; comorbidities (hypertension, diabetes, previous lung disease, CVDs); number of patients in the intensive care unit (ICU); number of patients requiring invasive ventilation (IV); lymphocyte number; serological markers (IL-6, CRP, Ferritin); and outcomes after treatment (improvement or stabilisation, ICU admission, and death). Wherever data were missing or inconsistent, the authors were contacted to obtain the necessary information.

Assessment of methodological quality

The quality of studies included in the quantitative analysis was assessed using the "star system" of the Newcastle-Ottawa Quality Assessment Scale (NOS) (12). The minimum and maximum scores that could be awarded were 0 stars and 9 stars, respectively (Suppl. Table S4). Studies that scored ≥7 stars were regarded as high quality. For case-series studies, we assessed the quality using the Quality Assessment Tool for Before-After (Pre-Post) Studies with No Control Group proposed by the National Heart, Lung, and Blood Institute–US Department of Health & Human Services (https://www.nhlbi.nih.gov/health-pro/guidelines/in- develop/cardiovascular-risk-reduction/tools/before-after). After scoring each item, an overall rate (good, fair, or poor) was assigned by each reviewer (Suppl. Table S5). The quality assessment was performed by two reviewers (OB and PR) and any disagreement was resolved by a third reviewer (RG) who re-evaluated the original study.

Statistical analysis

Pooled prevalence and their 95% confidence intervals (95% CI) were used to summarise the weighted effect size for each variable using the binary random-effects model, except for median age, IL-6 levels, and CRP levels, where a continuous random effect model was applied (13, 14). The relationship between mortality and treatment with TCZ was assessed using odds ratio (OR) and 95% CI as well as by Mantel-Haenszel estimates. A significant heterogeneity was expected among studies. Data were combined using random effect models, which assumes that the included studies have varying effect sizes, thus providing a conservative estimate of the overall effect. The Cochrane chi-square (Cochrane Q) test and I^2 test were carried out to analyse the heterogeneity among the results of different studies. An I^2 value <25% was considered indicative of no heterogeneity, while I^2>50% and/or p<0.05 indicated substantial heterogeneity (15). Meta-regression model analysis for the estimated pooled prevalence of mortality was conducted to investigate study heterogeneity (16). Heterogeneity was investigated by looking at a number of possible covariates that could affect the estimated pooled prevalence of mortality: age, male sex, hypertension, previous lung disease, diabetes, CVDs, patients in ICU before TCZ treatment, patients requiring IV before TCZ, CRP levels, and IL-6 levels, ferritin levels, lymphocytes. The extracted data were analysed using the statistical software R (v. 3.0.3; R Foundation for Statistical Computing, Vienna, Austria) and the Review Manager (RevMan) of the Cochrane Library (v. 5.3; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

Results

Study selection and characteristics

A total of 708 articles were retrieved by using the above-mentioned search strategy and, after screening titles and abstracts, 63 articles were selected for full-text assessment. After review, 25 studies were included in the qualitative and 22 studies were included in the quantitative analysis. All the studies were published during the COVID-19 outbreak, starting from March 26, 2020 to July 21, 2020, when we conducted this review. Eight out of those studies were conducted in Italy (17-24); seven in US (25-31); three in France (32-34); two in China (35, 36); one in Spain (37); one in Qatar (38); and one in Turkey (39). All these studies referred to the general population. Of the 23 included studies, 14 were single-arm studies, and 9 reported data from a control group. The main characteristics of the selected studies are reported in Table I. All included patients had a confirmed diagnosis of SARS-CoV-2 infection, per the results of real-time reverse transcriptase polymerase chain reaction (RT-PCR) from clinical nasopharyngeal swabs, except for one person included in the Turkish study (39). The inclusion criteria were similar in all studies and included all persons with at least one of the following characteristics: (i) respiratory rate, ≥30 breaths/min; (ii) peripheral capillary oxygen saturation (SpO_2), ≤93% while breathing room air; and (iii) PaO_2/FiO_2, ≤300 mmHg. Considering the fast spread-up of this virus and the high mortality rate observed in several Countries, many observational studies were performed and rapidly published, with a median time from receipt to acceptance of 6 days (40) to give medical information as soon as possible. Thus, the overall quality of selected studies is still poor, being many retrieved studies retrospectively designed and still waiting for randomised trials, which naturally need longer time to be concluded (Table I, Suppl. Tables S4, S5). Furthermore, the selected studies for this meta-analysis showed different outcomes, as reported in Supplementary Table S6, and this diversity, together with the different study design, may partially explain the results variability. The main clinical and demographic characteristics of TCZ-treated patients are reported in Table I.

Tocilizumab-treated patients: main outcomes and findings

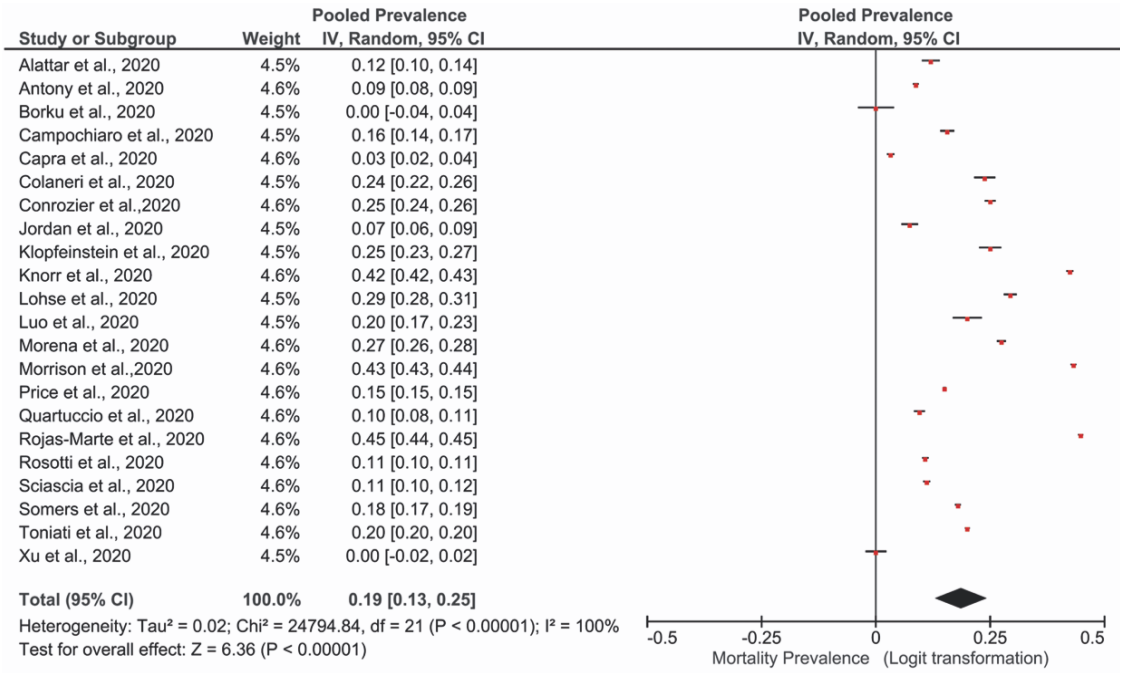
We assessed the mortality rate (22 studies) and the number of persons improved or stabilised (16 studies). With respect to the mortality rate, the estimated pooled prevalence was 19% (95% CI: 13–25), with a high heterogeneity (I^2=100%, p<0.00001) (Fig. 2). Meta-regression analysis was performed to investigate sources of heterogeneity and factors associated with the main outcome. The number of participants in ICU (meta-regression coefficient = 0.0046, p=0.002, adjusted R=51.13%), the numbers of participants with IV (meta-regression coefficient = 0.0037, p=0.0035, adjusted R^2 =24.05%) and the sera CRP levels (meta-regression coefficient = 0.0019, p=0.003, adjusted R^2=43.19%) showed significant positive association with the number of death, but these variables did not account for the high heterogeneity. (Suppl. Table S3, Suppl. Fig. S1).

As shown in Figure 3, TCZ treatment was associated with a significant reduction in the odds of mortality in TCZ-treated patients when compared with those treated using other therapies (OR=0.47, 95% CI: 0.22–0.98, p=0.04). A significant heterogeneity was observed among the studies (p for heterogeneity=0.004, I^2=68%), and among its

Table I. Main characteristics of included studies.

Author, year, country	Study type	Quality score	n	TCZ (n)	Age, mean (SD) or median (range)	Male (n)	Hyper-tension (n)	Lung disease (n)	Diabetes	CVDs (n)	ICU (n)	IV (n)	Lympho-cytes (×10^9/L)	IL-6 (pg/mL) (range or SD)	CRP (mg/L) (range or SD)	Ferritin (ng/mL) (range or SD)	Improved or stabilised (n)	Death (n)
Capra *et al*. 2020 Italy (21)	Retrospective	7§	85	IV, SC (62)	63 (54-73)	45	28	-	8	8	0	0	-	-	-	-	50	2
Price *et al*. 2020 USA (25)	-	7§	239	IV (153)	65 (23-92)	88	97	58	72	46	-	48	-	15.67) (6-34	135 (92-194)	-	122	23
Colaneri *et al*. 2020 Italy (17)	Retrospective	6§	112	IV (21)	62.33	19	8	0	2	2	-	-	0.60	-	21.38	-	-	5
Campochiaro *et al*. 2020 Italy (23)	Retrospective	9§	65	IV (32)	64±5.5	29	12	1	4	4	0	-	-	-	155±27	1400 (1027–2777)	22	5
Somers *et al*. 2020 USA (26)	-	5§	154	IV (78)	55 ±14.9	43	50	29	8	10		78	0.9 ±0.4	-	185 (112– 278)	1262 (738–1804)	44	14
Rojas-Marte *et al*. 2020 USA (27)	Retrospective	8§	193	- (96)	58.8±13.6	29	-	8	4	15	-	61	-	-	171±89	1023±934	-	43
Klopfeinstein *et al*. 2020 France (32)	Retrospective	9§	45	IV (20)	76.8 (52–93)	-	11	4	5	14	-	-	-	-	158 (61–309)	-	11	5
Quartuccio *et al*. 2020 Italy (20)	Retrospective	5§	111	- (42)	62.4±11.8	33	20	-	-	-	27	-	-	63.5 (37.25-135.5)	79.05 (47.8-186.22)	-	38	4
Rosotti *et al*. 2020 Italy (24)	Retrospective	8§	222	IV (74)	59 (51-71)	61	-	-	-	-	-	24	-	-	-	-	14	8
Alattar *et al*. 2020 Qatar (26)	Retrospective	Poor*	25	IV (25)	58 (50-63)	23	-	-	12	3	25	21	0.9 (0.7-1.1)	-	95.2 (49.8-204.4)	-	21	3
Lohse *et al*. 2020 France (33)	Retrospective	Poor*	34	IV (34)	75.3 (52-93)	24	18	4	6	10	-	-	0.87 (0.02-1.51)	-	146.0 (23.8-283.1)	1474.7 (156-6115)	24	10
Morrison *et al*. 2020 USA (28)	Retrospective	Fair*	81	IV (81)	64 (58–71)	56	60	15	37	23	74	70	-	22 (7.0–62)	168 (112–272)	1470 (885–2543)	46	35
Borku *et al*. 2020 Turkey (29)	Retrospective	Poor*	12	IV (12)	65.83±11.3	6	7	3	7	4	-	-	1.14±0.41	-	109.83±55.78	639.25±487.53	12	0
Conrozier *et al*. 2020 France (34)	Retrospective	Fair*	40	- (40)	-	-	-	-	-	-	-	-	-	-	-	-	-	10
Knorr *et al*. 2020 USA (29)	Retrospective	Poor*	66	IV (66)	61 (54.5-67)	41	49	11	28	-	-	18	-	-	174.3 (94.4-250.6)	1146 (753-2422)	-	28
Jordan *et al*. 2020 USA (30)	-	Fair*	27	- (27)	63 (51-75)	23	12	9	3	7	-	21	-	-	-	-	-	2
Luo *et al*. 2020 China (24)	Retrospective	Poor*	15	- (15)	73 (62-80)	12	9	-	4	3	-	-	-	46.8 (16,4-627.1)	126.9 (10.7-257.9)	-	11	3
Fernández-Ruiz *et al*. 2020 Spain (37)	Retrospective	Fair*	88	IV (88)	46.8±10.7	58	19	12	5	-	-	-	0.9±0.4	109.6 ±296.1	156±83	1.860 ±2.493	65	-
Morena *et al*. 2020 Italy (23)	Prospective	Fair*	51	IV (51)	50±5	40	15	5	6	25	9	6	0.8 (0.6-1.1)	116 (65-180)	189 (138-268)	-	37	14
Sciascia *et al*. 2020 Italy (19)	Prospective	Fair*	63	IV/SC (63)	62.6±12.5	56	24	3	6	5		5	-	-	-	-	-	7
Antony *et al*. 2020 USA (31)	-	Fair*	80	IV (80)	63 (51-72)	45	47	-	37	-	-	-	-	342.50 (78.25-666.25)	11 (6-18.75)	595 (311.25-1022.50)	-	7
Toniati *et al*. 2020 Italy (18)	Prospective	Poor*	100	IV (100)	62 (57-71)	88	46	-	17	16	43	57	0.62 (0.41-0.84)	41 (10-102)	113 (45-169)	1689 (981-3533)	77	20
Xu *et al*. 2020 China (23)	Retrospective	Poor*	21	IV (21)	56.8 (25–88)	18	9	2	5	4		2	-	153.44±296.63	75.06±66.80	-	21	0

§Newcastle-Ottawa scale, ranged 0-9, *Quality Assessment Tool for Before-After (Pre-Post) Studies with No Control Group proposed by the National Heart, Lung, and Blood Institute - US Department of Health & Human Services (https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/before-after). n: number of patients; SD: standard deviation; CVDs: cardiovascular diseases; ICU: intensive care unit; IV: invasive ventilation; IL-6: interleukin-6; CRP: C-reactive protein; TCZ: Tocilizumab. IL-6 and CRP value are reported as mean (SD) or median (range).



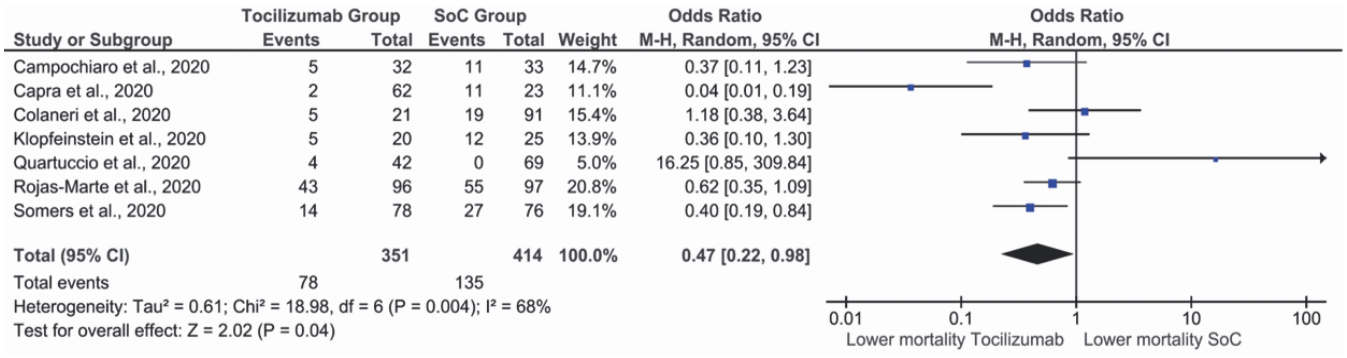


Fig. 2. Pooled prevalence of mortality in tocilizumab-treated patients.

Fig. 3. Meta-analysis of the mortality between tocilizumab-treated persons and other treatments (SoC)-treated persons.
Meta-analysis of the mortality between tocilizumab-treated persons and other treatments (SoC)-treated persons. The size of squares is proportional to the weight of each study. Horizontal lines indicate the 95% CI of each study; diamond, the pooled estimate with 95% CI.
n: number of persons at baseline; OR: odds ratio; SoC: standard of care.

sources, at the meta-regression analysis, we found the number of patients with diabetes (meta-regression coefficient = -0.28, p=0.045, adjusted R^2=36.75%), the number of patients in ICU (meta-regression coefficient = 0.18, p=0.042, adjusted R^2=53.06%), and the number of patients requiring IV (meta- regression coefficient = 0.033, p=0.043, adjusted R^2=43.93%) were significant associated with mortality. Although these factors are associated with the main outcome, they cannot fully explain the high heterogeneity observed.

As shown in Supplementary Figure S2, a publication bias was revealed by a clear asymmetry in the funnel plot of studies analysing the overall estimates mortality between TCZ-treated patients and patients not treated with TCZ. Although the trim and fill analysis estimated the absence of one study in the left side of the distribution (Suppl. Fig. S2), the adjusted odds model was still significant (p=0.019), confirming the reduced mortality in TCZ-treated patients. The estimated pooled prevalence of patients who improved or remained stable, after receiving TCZ treatment, was 71% (95%; CI: 62-81), with a high heterogeneity (I^2=91%; p<0.0001).

All data are summarised in Table II and Supplementary Table S3. Briefly, prevalence of male gender was 71% (95%; CI: 64–78%) with high heterogeneity (I^2=88%; p<0.0001) (22 studies), and the median age ranged between 59 and 64 years, with an estimated pooled mean of 61, with high heterogeneity (I^2=88%; p<0.0001) (21 studies). Among the reported co-morbidities, we selected and analysed hypertension, diabetes, previous lung diseases, and CVDs. The estimated pooled prevalence for hypertension was very high, 51% (95%; CI: 44–57) with high heterogeneity (I^2=82%; p<0.0001) (20 studies). Diabetes showed an estimated pooled prevalence of 25% (95%; CI: 17–32) (21 studies); CVDs showed an estimated pooled prevalence of 24% (95%; CI: 17–30) (18 studies); and lung diseases showed an estimated pooled prevalence of 19% (95%; CI: 12–26) (16 studies). All showed a high degree of heterogeneity. The pooled prevalence of patients in the ICU was 45%

Table II. Meta-analysis outcomes (random-effects model).

Variable	n of studies	Prevalence (%) or mean	95% CI	n	I^2	t^2	*p*	Q
Male gender	23	71	64-78	1460	87.99	0.028	<0.0001	186.24
Age (year)	23	61.64	59.45-63.82	1460	88.11	19.01	<0.0001	286.86
Hypertension	20	51	44-57	1285	81.68	0.017	<0.0001	110.00
Diabetes	21	25	17-32	1364	89.32	0.033	<0.0001	213.32
CVDs	18	24	17-30	1130	82.29	0.019	<0.0001	78.60
Lung disease	16	19	12-26	1082	86.47	0.024	<0.0001	126.69
Participants in ICU	7	45	14-76	393	98.47	0.294	0.0006	337.02
Participants with IV	14	44	26-61	1136	98.10	0.164	<0.0001	582.28
Participants improved or stabilised after TCZ	16	71	62-81	888	91.25	0.048	<0.0001	156.13
Mortality rate	22	19	13-25	1193	100	0.02	<0.00001	129.00

CI 95%: confidence interval 95%; n: sample size; I^2: Index for the degree of heterogeneity; t^2: tau-squared, measure of heterogeneity; *p*: *p*-value; n: number; CVDs: cardiovascular diseases; IV: invasive ventilation; TCZ: Tocilizumab; IL-6: interleukin-6; CRP: C-reactive protein.

(95%; CI: 14–76) (7 studies). As far as the number of patients requiring IV were concerned, the pooled estimated prevalence was 44% (95%; CI: 26–61) (14 studies), with high heterogeneity.

Discussion

Severe COVID-19 is associated with high mortality in different Countries and health-care systems are facing this pandemic without specific anti-viral treatments and/or vaccines. Thus, data emerging from available literature are crucial to help physicians in the decision making, how to treat these patients at front-line, every-day. In this study, analysing data derived from 1520 TCZ-treated patients, the estimated pooled prevalence of mortality (19%), is largely lower than the mortality reported so far (41-44). In fact, a previous retrospective analysis, including 1438 hospitalised patients, showed a mortality rate of 25.7%, and, in the same study, as far as non-ICU patients were considered, the mortality rate was 19.6% (41). These data confirmed the important therapeutic effect of TCZ, in COVID-19 patients, decreasing the mortality of the sub-group at higher risk (ICU and IV patients) to the same level of patients with a mild disease, not needing intensive care. Furthermore, a large variability concerning mortality in ICU patients, has been reported ranging from 26% (42) to 78% (43). The results of pooled data clearly show that higher the number of patients needing intensive care hospitalisation (ICU and/or IV) higher the mortality rate, thus confirming what already reported, since probably affected by a more severe disease (41), and with a higher risk for poor prognosis (45). As far as the laboratory variables are concerned, only CRP sera values showed a positive association with the pooled mortality rate. CRP levels were found to be higher in severe COVID-19 patients when compared to patients with a mild disease (46). Furthermore, it has been reported that higher CRP level on admission may be considered as an independent factor of disease severity, being the higher values associated with poor prognosis (47). Surprisingly, in our analysis, we did not find any association between IL-6 sera value at baseline and the mortality rate, after TCZ treatment. It must be pointed out that only 9 out of 23 included studies reported IL-6 values before the treatment. Furthermore, no one of studies considered the prognostic value of IL-6 as primary end-point to evaluate the response to TCZ treatment. At present, it has been proposed that higher IL-6 sera values, in COVID-19 patients, are associated with early worsening and negative outcome (48-51). On these bases, it is still matter of debate the possible role of IL-6 in predicting TCZ response. More than 70% of TCZ-treated patients showed rapid improvement and/or stabilisation of clinical conditions, again confirming the usefulness of TCZ in the management of severe COVID-19.

As far as the OR for mortality rate was concerned, TCZ-treated patients showed a significant lower OR when compared with patients treated with other therapies; taking together all these results our paper supports the choice of IL-6 inhibition for controlling the CSS in severe COVID-19 patients, as suggested from many Authors (52-54). The mean age of TCZ-treated patients was 61 (59–64) years, mirroring what observed the available literature (42), whereas our data failed to identify any relationship between old-age and mortality (55). In our analysis the TCZ-treated patients were predominantly male (71%), and hypertension was the most common co-morbidity, with a pooled estimated prevalence of 51% (45), followed from diabetes, whose estimated prevalence was 25%. In this analysis, among all the assessed co-morbidities, only diabetes, seems to influence the mortality rate in TCZ-treated patients. Of note, the analysis of our patients showed a higher prevalence of diabetes when compared to the prevalence reported in Chinese cohort (56). Interestingly, diabetes was suggested as a negative prognostic factor also for ARDS development in COVID- 19 patients (57), strongly associated with the prevalence of deaths (58, 59).

To our knowledge, this systematic review and meta-analysis is the first report to provide a comprehensive analysis of the demographic and clinical findings, co-morbidities, and laboratory abnormalities associated with mortality in COVID-19 patients treated with TCZ. We analysed data from 22 studies with 1520 TCZ-treated patients from Italy and China – the two countries with the most severe outbreak during the early phase – US, Spain, France, Turkey, and Qatar. Despite the lack of high-quality published data, our find-

ings may be considered robust (owing to the pooled results) after combining all the studies by using a random-effects model. We are aware that our results may be influenced by the lack of randomised control studies, as well as the small number of available studies, mainly retrospective. The majority of the included studies were conducted in different settings by selecting different patient populations (ICU and non-ICU persons), and also with different TCZ dosages and routes of administration (Suppl. Table S6). Furthermore, even when different studies shared similar inclusions criteria, the timing for TCZ administration was different, strongly confirming the need of a common therapeutic strategy in this setting (60-61). Therefore, the overall generalisability of the meta-analysis results must be interpreted with caution. On the other hand, to tackle this dramatic pandemic, a better knowledge about drugs potentially helpful in the treatment of COVID-19 is an urgent need. In this setting, a deeper understanding of the role of TCZ in the treatment of severe COVID-19 may allow physicians to reduce the latency in the therapeutic decision and the health systems how to correctly allocate medical resources.

Conclusions

The SARS-CoV-2 pandemic is still prevalent in many countries worldwide, heavily burdening the healthcare systems, and consuming a large amount of resources. In this meta-analysis, we found that the mortality pooled prevalence in COVID-19 patients treated with TCZ is lower than the overall mortality in those that underwent different therapies. Additional data will be required to enhance the quantitative analysis about the mortality rate in patients with severe COVID-19 treated with TCZ and the possible associated risk factors. In conclusion, our data may provide important clinical information to physicians directly tackling the COVID-19 outbreak and help them with better therapeutic decision making.

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References

1. CHEN G, WU D, GUO W *et al*.: Clinical and immunological features of severe and moderate coronavirus disease 2019. *J Clin Invest* 2020; 130: 2620-9.
2. RUAN Q, YANG K, WANG W, JIANG L, SONG J: Clinical predictors of mortality due to COVID- 19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med* 2020; 46: 846-8.
3. TAY MZ, POH CM, RÉNIA L, MACARY PA, NG LFP: The trinity of COVID-19: immunity, inflammation and intervention. *Nat Rev Immunol* 2020; 20: 363-74.
4. CAO X: COVID-19: immunopathology and its implications for therapy. *Nat Rev Immunol* 2020; 20: 269-70.
5. RUSCITTI P, BERARDICURTI O, IAGNOCCO A, GIACOMELLI R: Cytokine storm syndrome in severe COVID-19. *Autoimmun Rev* 2020; 102562.
6. LE RQ, LI L, YUAN W *et al*.: FDA Approval Summary: Tocilizumab for treatment of chimeric antigen receptor T cell-induced severe or life-threatening cytokine release syndrome. *Oncologist* 2018; 23: 943-7.
7. CHOY EH, DE BENEDETTI F, TAKEUCHI T, HASHIZUME M, JOHN MR, KISHIMOTO T: Translating IL-6 biology into effective treatments. *Nat Rev Rheumatol* 2020; 16: 335-45.
8. MICHOT JM, ALBIGES L, CHAPUT N *et al*.: Tocilizumab, an anti-IL6 receptor antibody, to treat Covid-19-related respiratory failure: a case report. *Ann Oncol* 2020; 31: 961-4.
9. XU CY, LU SD, YE X *et al*.: Combined treatment of tocilizumab and chloroquine on severe COVID-19: a case report. *QJM* 2020; 113: 569-72.
10. ZHANG X, SONG K, TONG F *et al*.: First case of COVID-19 in a patient with multiple myeloma successfully treated with tocilizumab. *Blood Adv* 2020; 4: 1307-10.
11. MOHER D, LIBERATI A, TETZLAFF J, ALTMAN DG; PRISMA GROUP. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009; 6: e1000097.
12. DEEKS JJ, DINNES J, D'AMICO R *et al*.: Evaluating non-randomised intervention studies. *Health Technol Assess* 2003; 7: iii-173.
13. VIECHTBAUER W: Conducting meta-analyses in R with the metafor package. *J Stat Software* 2010 May 5 [Online ahead of print].
14. KONTOPANTELIS E, REEVES D: Performance of statistical methods for meta-analysis when true study effects are non-normally distributed: a comparison between DerSimonian-Laird and restricted maximum likelihood. *Stat Methods Med Res* 2012; 21: 657-9.
15. HIGGINS JP, THOMPSON SG, DEEKS JJ, ALTMAN DG: Measuring inconsistency in meta-analyses. *BMJ* 2003; 327: 557-60.
16. COLDITZ GA, BURDICK E, MOSTELLER F: Heterogeneity in meta-analysis of data from epidemiologic studies: a commentary. *Am J Epidemiol* 1995; 142: 371-82.
17. COLANERI M, BOGLIOLO L, VALSECCHI P *et al*.: Tocilizumab for treatment of severe COVID-19 patients: preliminary results from SMAtteo COvid19 REgistry (SMACORE). *Microorganisms* 2020; 8: E695.
18. TONIATI P, PIVA S, CATTALINI M *et al*.: Tocilizumab for the treatment of severe COVID-19 pneumonia with hyperinflammatory syndrome and acute respiratory failure: A single center study of 100 patients in Brescia, Italy. *Autoimmun Rev* 2020; 102568.
19. SCIASCIA S, APRÀ F, BAFFA A *et al*.: Pilot prospective open, single-arm multicentre study on off-label use of tocilizumab in patients with severe COVID-19. *Clin Exp Rheumatol* 2020; 38: 529-32.
20. QUARTUCCIO L, SONAGLIA A, MCGONAGLE D *et al*.: Profiling COVID-19 pneumonia progressing into the cytokine storm syndrome: results from a single Italian Centre study on tocilizumab versus standard of care. *J Clin Virol* 2020; 129: 104444.
21. CAPRA R, DE ROSSI N, MATTIOLI F *et al*.: Impact of low dose tocilizumab on mortality rate in patients with COVID-19 related pneumonia. *Eur J Intern Med* 2020; 76: 31-5.
22. MORENA V, MILAZZO L, ORENI L *et al*.: Off-label use of tocilizumab for the treatment of SARS-CoV-2 pneumonia in Milan, Italy. *Eur J Intern Med* 2020; 76: 36-42.
23. CAMPOCHIARO C, DELLA-TORRE E, CAVALLI G *et al*.: Efficacy and safety of tocilizumab in severe COVID-19 patients: a single-centre retrospective cohort study. *Eur J Intern Med* 2020; 76: 43-49.
24. ROSSOTTI R, TRAVI G, UGHI N *et al*.: Safety and efficacy of anti-il6-receptor tocilizumab use in severe and critical patients affected by coronavirus disease 2019: a comparative analysis. *J Infect* 2020; 81: e11-e17.
25. PRICE CC, ALTICE FL, SHYR Y *et al*.: Tocilizumab treatment for cytokine release syndrome in hospitalized COVID-19 patients: survival and clinical outcomes. *Chest* 2020; 158: 1397-408.
26. SOMERS EC, ESCHENAUER GA, TROOST JP *et al*.: Tocilizumab for treatment of mechanically ventilated patients with COVID-19. *Clin Infect Dis* 2020 Jul 11 [Online ahead of print].
27. ROJAS-MARTE G, KHALID M, MUKHTAR O *et al*.: Outcomes in patients with severe COVID-19 disease treated with tocilizumab - a case-controlled study. *QJM* 2020; 113: 546-50
28. MORRISON AR, JOHNSON JM, GRIEBE KM *et al*.: Clinical characteristics and predictors of survival in adults with coronavirus disease 2019 receiving tocilizumab. *J Autoimmun* 2020; 114: 102512.
29. KNORR JP, COLOMY V, MAURIELLO CM, HA S: Tocilizumab in patients with severe COVID-19: A single-center observational analysis. *J Med Virol* 2020; Jun 17 [Online ahead of print].
30. JORDAN SC, ZAKOWSKI P, TRAN HP *et al*.: Compassionate use of tocilizumab for treatment of SARS-CoV-2 pneumonia. *Clin Infect Dis* 2020 Jun 23 [Online ahead of print].
31. ANTONY SJ, DAVIS MA, DAVIS MG *et al*.: Early use of tocilizumab in the prevention of adult respiratory failure in SARS-CoV-2 infections and the utilization of interleukin-6 levels in the management. *J Med Virol* 2020 Jul 9 [Online ahead of print].
32. KLOPFENSTEIN T, ZAYET S, LOHSE A *et al*.: Tocilizumab therapy reduced intensive care unit admissions and/or mortality in COV-

ID-19 patients. *Med Mal Infect* 2020; 50: 397-400
33. LOHSE A, KLOPFENSTEIN T, BALBLANC JC *et al*.: Predictive factors of mortality in patients treated with tocilizumab for acute respiratory distress syndrome related to coronavirus disease 2019 (COVID-19). *Microbes Infect* 2020; 22: 500-503.
34. CONROZIER T, LOHSE A, BALBLANC JC *et al*.: Biomarker variation in patients successfully treated with tocilizumab for severe coronavirus disease 2019 (COVID-19): results of a multidisciplinary collaboration. *Clin Exp Rheumatol* 2020; 38: 742-7.
35. XU X, HAN M, LI T *et al*.: Effective treatment of severe COVID-19 patients with tocilizumab. *Proc Natl Acad Sci USA* 2020; 117: 10970-5.
36. LUO P, LIU Y, QIU L, LIU X, LIU D, LI J: Tocilizumab treatment in COVID-19: a single center experience. *J Med Virol* 2020; 92: 814-18.
37. FERNÁNDEZ-RUIZ M, LÓPEZ-MEDRANO F, PÉREZ-JACOISTE ASÍN MA *et al*.: Tocilizumab for the treatment of adult patients with severe COVID-19 pneumonia: a single-center cohort study. *J Med Virol* 2020 Jul 16 [Online ahead of print].
38. ALATTAR R, IBRAHIM TBH, SHAAR SH *et al*.: Tocilizumab for the treatment of severe coronavirus disease 2019. *J Med Virol* 2020 May 5 [Online ahead of print].
39. BORKU UYSAL B, IKITIMUR H, YAVUZER S *et al*.: Tociluzumab challenge: A series of cytokine storm therapy experience in hospitalized Covid-19 pneumonia patients. *J Med Virol* 2020 Jun 2 [Online ahead of print].
40. PALAYEW A, NORGAARD O, SAFREED-HARMON K *et al*.: Pandemic publishing poses a new COVID-19 challenge. *Nat Hum Behav* 2020; 4: 666-9.
41. ROSENBERG ES, DUFORT EM, UDO T *et al*.: Association of treatment with hydroxychloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in New York State. *JAMA* 2020; 323: 2493-502.
42. GRASSELLI G, ZANGRILLO A, ZANELLA A *et al*.: Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy. *JAMA* 2020; 323: 1574-81.
43. ZHOU F, YU T, DU R *et al*.: Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020; 395: 1054-62.
44. DOCHERTY AB, HARRISON EM, GREEN CA *et al*.: Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. *BMJ* 2020; 369: m1985.
45. PRANATA R, LIM MA, HUANG I, RAHARJO SB, LUKITO AA: Hypertension is associated with increased mortality and severity of disease in COVID-19 pneumonia: A systematic review, meta-analysis and meta-regression. *J Renin Angiotensin Aldosterone Syst* 2020; 21: 1470320320926899.
46. WANG L: C-reactive protein levels in the early stage of COVID-19. *Med Mal Infect* 2020; 50: 332-4.
47. LUO X, ZHOU W, YAN X *et al*.: Prognostic value of C-reactive protein in patients with COVID-19. *Clin Infect Dis* 2020 May 23 [Online ahead of print].
48. CECCONI M, PIOVANI D, BRUNETTA E *et al*.: Early predictors of clinical deterioration in a cohort of 239 patients hospitalized for Covid-19 infection in Lombardy, Italy. *J Clin Med* 2020; 9: E1548.
49. BURIAN E, JUNGMANN F, KAISSIS GA *et al*.: Intensive care risk estimation in COVID-19 pneumonia based on clinical and imaging parameters: experiences from the Munich cohort. *J Clin Med 2020*; 9: E1514.
50. TIAN W, JIANG W, YAO J *et al*.: Predictors of mortality in hospitalized COVID-19 patients: a systematic review and meta-analysis. *J Med Virol* 2020 May 22 [Online ahead of print].
51. AZIZ M, FATIMA R, ASSALY R: Elevated interleukin-6 and severe COVID-19: a meta-analysis. *J Med Virol* 2020 Apr 28 [Online ahead of print].
52. RUSCITTI P, BERARDICURTI O, DI BENEDETTO P *et al*.: Severe COVID-19, another piece in the puzzle of the hyperferritinemic syndrome. An immunomodulatory perspective to alleviate the storm. *Front Immunol* 2020; 11: 1130.
53. CORTEGIANI A, IPPOLITO M, GRECO M *et al*.: Rationale and evidence on the use of tocilizumab in COVID-19: a systematic review. *Pulmonology* 2020 Jul 20 [Online ahead of print].
54. CHIBBER P, HAQ SA, AHMED I, ANDRABI NI, SINGH G: Advances in the possible treatment of COVID-19: A review. *Eur J Pharmacol* 2020; 883: 173372.
55. DU RH, LIANG LR, YANG CQ *et al*.: Predictors of mortality for patients with COVID-19 pneumonia caused by SARS-CoV-2: a prospective cohort study. *Eur Respir J* 2020; 55: 2000524.
56. SINGH AK, GUPTA R, GHOSH A, MISRA A: Diabetes in COVID-19: Prevalence, pathophysiology, prognosis and practical considerations. *Diabetes Metab Syndr* 2020; 14: 303-10.
57. WU C, CHEN X, CAI Y *et al*.: Risk factors associated with acute respiratory distress syndrome and death in patients with Coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med* 2020; 180: 1-11.
58. YANG X, YU Y, XU J *et al*.: Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med* 2020; 8: 475-81.
59. CHEN T, WU D, CHEN H *et al*.: Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *BMJ* 2020; 368: m1091.
60. FERRO F, ELEFANTE E, PUXEDDU I *et al*.: COVID-19: the new challenge for rheumatologists. First update. *Clin Exp Rheumatol* 2020; 38: 373-82.
61. FERRO F, ELEFANTE E, BALDINI C *et al*.: COVID-19: the new challenge for rheumatologists. *Clin Exp Rheumatol* 2020; 38: 175-80.