Review

Efficacy and safety of tocilizumab in the management of COVID-19: a systematic review and meta-analysis of observational studies

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ABSTRACT

Objective. *This systematic review and meta-analysis was aimed to evaluate the efficacy and safety of tocilizumab (TCZ) in treating severe coronavirus disease 2019 (COVID-19).*

Methods. *The electronic search was made using PubMed, Scopus, CENTRAL, and Google scholar to identify the retrospective observational reports. The studies published from 01 January 2020 to 30th October 2020. Participants were hospitalised COVID-19 patients. Interventions included tocilizumab versus placebo/standard of care. The comparison will be between TCZ versus standard of care (SOC)/placebo. Inconsistency between the studies was evaluated with I^2 and quality of the evidences were evaluated by Newcastle-Ottawa scale.*

Results. *Based on the inclusion criteria there were 24 retrospective studies involving 5686 subjects were included. The outcomes of the meta-analysis have revealed that the TCZ has reduced mortality (M-H, RE-OR -0.11(-0.18 – -0.04) 95% CI, p=0.001, I^2 =88%) and increased the incidences of super-infections (M-H, RE-OR 1.49(1.13–1.96) 95% CI, p=0.004, I^2=47%). However, there is no significant difference in ICU admissions rate (M-H, RE-OR -0.06(-0.23–0.12), I^2=93%), need for mechanical ventilation (M-H, RE-OR of 0.00(-0.06–0.07), I=74%), LOS (IV -2.86(-0.91–3.38), I^2=100%), LOS-ICU (IV: -3.93(-12.35–4.48), I^2=100%), and incidences of pulmonary thrombosis (M-H, RE-OR 1.01 (0.45–2.26), I^2=0%) compared to SOC/control.*

Conclusion. *Based on cumulative low-to-moderate certainty evidence shows that TCZ could reduce the risk of mortality in hospitalised patients. However, there is no statistically significant difference observed between the TCZ and SOC/control groups in other parameters.*

Introduction

Coronavirus diseases (COVID-19) is a viral disease caused by severe acute respiratory syndrome corona virus-2 (SARS-CoV-2) that originated from Wuhan city of Hubei province in China in December 2019 (1). Globally, it has caused a significant burden on public health through a drastic increase in the morbidity and mortality rate (2). The available evidence suggests that most of the infected patients will remain asymptomatic or develop mild symptoms, however nearly 20% of the infected individuals would develop severe pneumonia and respiratory distress syndrome (ARDS) that further progress to cytokine storm syndrome and induced end-organ failure (3). Interestingly, the United States Food and Drug Administration (US-FDA) has approved the drugs such as remdesivir (4), bamlanivimab (5), and dexamethasone (6) for the treatment of hospitalised patients with COVID-19. Further, the drugs such as decitabine (7), duvelisib (8), and infliximab (9) are currently under clinical development phase for the treatment of COVID-19. In this context, it is well-known that interleukin-6 (IL-6) is a pleiotropic cytokine that plays a pivotal role in immune-regulation, inflammation, and infection (10-12). Noteworthy, the elevated levels of IL-6 in the blood is highly correlated with the mortality rate in the COVID-19 infected patients (13, 14). The activation of the IL-6 amplifier would induce cytokine storm, a hallmark of dysregulated inflamma-

tion, and thus inhibition or blockade of IL-6 amplifier would alleviate cytokine storm in COVID-19 (13-15). In these lines many studies have reported that TCZ administration could stabilise the health status of COVID-19 patients by improving respiratory functions, reducing CRP levels, and improved health deteriorations due to COVID-19 (12). Besides, there are multiple case study series, retrospective and prospective study reports available on the therapeutic benefits of TCZ in COVID-19. As of now, there are five randomised controlled trials (RCTs) reported on the use of TCZ in COVID-19 (RCT-TCZ-COVID-19 NCT04346355, CORIMUNO-19 NCT04331808, BACC Bay Tocilizumab Trial NCT04356937, COVACTA NCT04320615, REMAP-CAP NCT02735707, and EMPACTA NCT04372186), the low number of subject enrolments In those studies are considered as major limitations and authors have highlighted the need for multicentric RCTs involving a higher number of subjects to determine the safety and efficacy of tocilizumab in COVID-19. In this context, there are several randomised controlled trials registered and under progress to evaluate the clinical benefits of TCZ in alleviating COVID-19 and associated health problems (phase II; NCT04317092, NCT04445272, NCT04377659, NCT04330638, NCT04345445) (16).

With this background, the present study was undertaken to evaluate the clinical benefits of TCZ when administered alone and in combination with standard of care (SOC) and/or placebo in reducing the COVID-19-induced mortality, ICU admissions, MV, LOS, LOS-ICU, super-infections, and pulmonary thrombosis.

Methodology

A detailed literature search was performed using electronic databases such as PubMed, Science direct, CENTRAL (Cochrane Central Register of Controlled Trials (RCTs), and google scholar to identify the clinical reports (retrospective). The keywords such as 'Coronavirus disease 2019' OR 'Coronavirus infection' OR 'Coronavirus' OR 'SARS COV-2' OR 'nCOV 2019' 'Severe acute respiratory syndrome COV 2' AND 'Tocilizumab' OR 'Interleukin-6 inhibitors' OR 'Cytokine storm' and 'COVID-19 treatment' were used. Grey (unpublished) literature was searched in the following trial registries: US National Institutes of Health (NIH; https://clinicaltr ials.gov/) and the WHO International Clinical Trials Registry Platform (ICTRP; https://apps.who.int/trialsearch/). Further, the pre-print servers such as Research Square, bioRxiv.org, and medRxiv were also considered while searching the grey literature. Besides, authors have approached the domain experts, seeking their suggestions and inputs in identifying the additional studies (if any) relevant to the topic. The search was not restricted to any publication language or status of the trial. Furthermore, the reference lists of all relevant articles were hand-searched to find additional studies. An example of a search strategy using PUBMED and Google Scholar has been highlighted in the Supplementary Appendix.

Inclusion criteria

The studies published from 01 January 2020 to 30th October 2020 involving comparison of TCZ group with SOC/control treatment group were included. The studies included in this work involves RT-PCR confirmed cases of COVID-19 (Population), having tocilizumab and corresponding SOC/control as interventions (Intervention), comparison between tocilizumab versus SOC/control (Comparison) for the parameter of interest, the evaluations such as Mortality, ICU admissions, MV, LOS, LOS-ICU, super-infections and pulmonary thrombosis (Outcomes) were included in the study.

Exclusion criteria

1. Studies reporting incomplete data.
2. Single-arm studies.
3. Duplicates, case reports, case series were excluded.
4. *In-vitro* and pre-clinical studies
5. Studies reporting qualitative outcomes without numerical data

The authors of the shortlisted articles were approached through e-mail wherever additional clarification was required. Such as allocation of subjects to control and treatment group, Baseline evaluations, confounding variables, classification of interventions, if there are any deviations in the intended interventions, measurement of outcomes, data handling, if there is any missing data, reason for missing of data (like selective reporting), treatment details like details of standard of care (SOC) and tocilizumab, the adjustments in the analysis, and so on. The exclusion was executed upon mutual discussion and agreement of all the authors as per exclusion criteria already mentioned.

Quality assessment and risk of bias analysis for included studies

All the included studies were subjected to the quality assessment using the Newcastle-Ottawa scale and also evaluated for risk of bias using the Cochrane Collaboration tool to assess The Risk of Bias in Non-randomised Studies of Interventions (ROBINS-I).

Parameters

The parameters related to COVID-19 such as mortality, ICU (intensive care unit) ward admission rate, the need for ventilation, length of hospital stay (LOS), length of hospital stay in the ICU (LOS-ICU), and the incidences events such as super-infections, fungaemia, bacteraemia, pneumonia, and pulmonary thrombosis were evaluated as the primary outcomes. The comparison will be between TCZ and standard care/placebo/control.

Article selection, data extraction, and analysis

The article selection and data extraction was performed by two reviewers separately based on the inclusion and exclusion criteria listed above. The analysis was carried out at three levels namely on title, abstract and full-text level. Any disagreement was resolved by discussing it with the third reviewer. Two authors have individually extracted the data such as details of participants, methods, interventions, frequency/duration of treatment, outcome measurements, and adverse effects from the included studies. For studies that reported results only in graphical form, numerical values from the graphs

were extracted using Adobe® Reader® XI inbuilt measuring tool, version 11.0.06, (Adobe Systems Incorporated, San Jose [California]). Any disagreement was resolved by discussing it with the third reviewer.

Statistical analysis

Review Manager (RevMan v. 5.3; Nordic Cochrane Centre [Cochrane Collaboration], Copenhagen, Denmark; 2014) shall be used to analyse the data. For continuous, variables, inverse variance (IV) was estimated using the random-effects model with a mean difference (MD) or standardised mean difference (SMD) as an effect measure and for the dichotomous variables, the Mantel-Haenszel (M-H) statistic was estimated using a random-effects model with an odds ratio (OR) as the effect measure. Heterogeneity was calculated with the I^2 statistic. This test estimates the percentage of variation between study results that is due to heterogeneity rather than sampling error. I^2 of less than 40% is considered unimportant while that of more than 40% is viewed as moderate to considerable heterogeneity.

Results

A total of 1425 articles were identified based on the online search, of which 24 articles involving 5676 participants were selected for systematic review and meta-analysis (a list of excluded studies based on the full-text screening is given in Supplementary Table S1). The PRISMA flow chart of the studies selected is given in Figure 1. Only retrospective studies were selected for the analysis; the characteristics of the included studies are summarised in Table I. In all the included studies, TCZ was common and the effect of TCZ was compared with the control group; while in few studies, both standard treatment and TCZ groups had background/previously received either antibiotics, antiviral drugs and corticosteroids, and oxygen which are considered as the standard of care (SOC), and in these studies, the comparison was made between TCZ + SOC *versus* SOC alone, here the SOC alone is considered as placebo. In the studies where multiple doses of TCZ was used, the response for mid-dose was considered for analysis. In this study, the parameters such as mortality, ICU ward admission rate, need for mechanical ventilation (MV), length of hospital stay (LOS), length of hospital stay in ICU (LOS-ICU) and incidences of events such as super-infections, fungaemia, bacteraemia, pneumonia, and pulmonary thrombosis were compared between TCZ treatment *versus* control/SOC groups in COVID-19 positive patients.

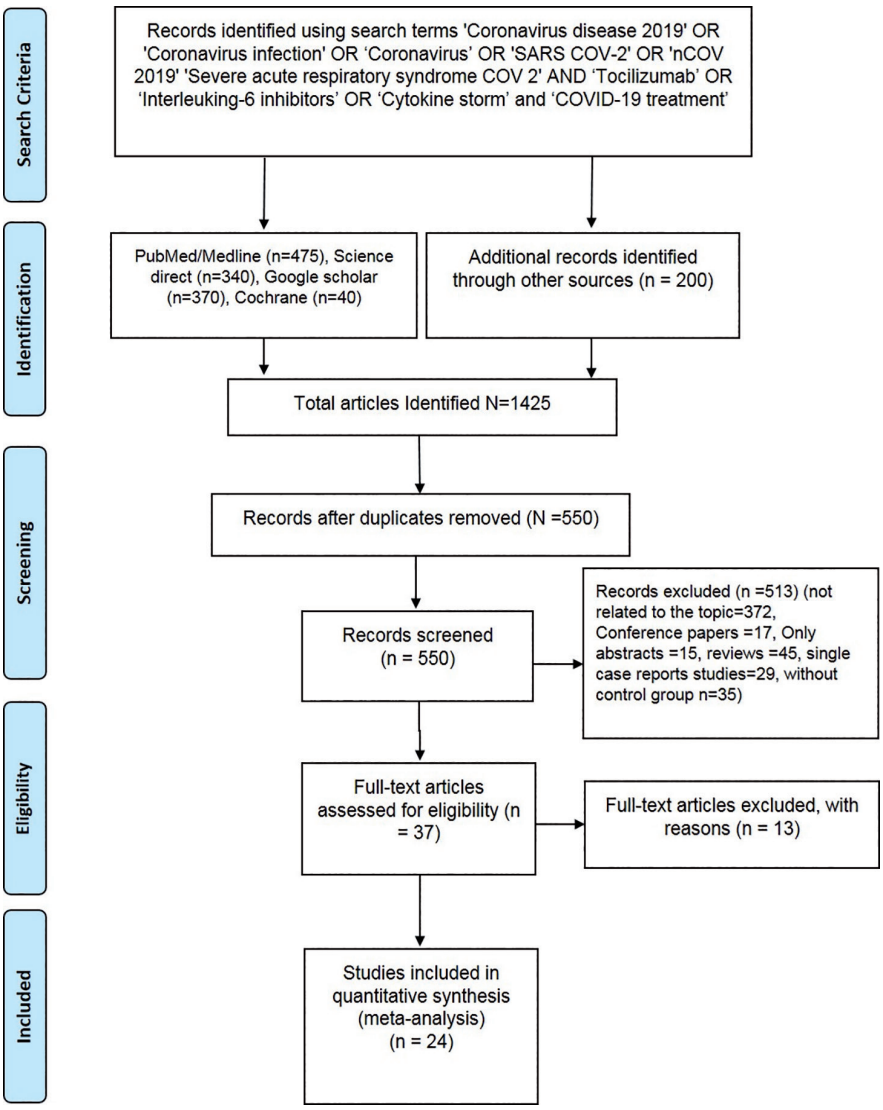

Fig. 1. PRISMA Flow chart.

Quality assessment and risk of bias

All the included studies have passed the quality assessment and showed a low risk of bias. The quality assessment and risk of bias (RoB) assessment for all the 24 included observational studies are given in Supplementary Tables S2 and S3, respectively.

Efficacy

The improvement in the parameters such as mortality, ICU ward admission rate, need for MV, length of hospital stay (LOS), and Length of Hospital Stay in ICU (LOS-ICU) were considered for evaluating and concluding the efficacy of TCZ compared to control group in COVID-19 positive patients.

Mortality rate

The COVID-19 positive patients treated with TCZ have shown a mortality rate of 24.3% (448/1841), whereas the control group received SOC has a mortality rate of 31.2% (1079/3454). The outcomes of the meta-analysis has revealed that the TCZ treatment has reduced the mortality rate (Mantel-Haenszel (M-H), random effects odds

Table I. Description of Included studies.

Sl. No	Author name	Study design	The population included in the study	Total no. of patients (Control + TCZ)	Control group	Tocilizumab (TCZ) Treatment	Parameters	Funding	Adjustments in The analysis (statistical analysis)
1	Andrew IP et al., 2020 [18]	Retrospective observational, multicentre cohort	1) positive SARS-CoV-2 patients 2) hospitalised within the time frame of March 1, 2020, until May 5, 2020, 3) non-pregnant, 4) not on a randomised clinical trial, and 5) did not die during the first day of hospitalisation, and 5) were not discharged to home within 24hours	n=547	n=413, SOC (HCQ, 500mg + AZT-500mg orally)	n=134, TCZ	Mortality, oxygenation, ferratin, D-dimer, ICU admission and	Nil	Chi-square test and Unadjusted Kaplan-Meier estimates
2	Biran N *et al*., 2020 [44]	Multicentre retrospective cohort	1). adult patients (aged ≥18 years) with a positive SARS-CoV-2 diagnosis by RT-PCR. 2) hospitalised during the study period and required ICU support	n=764	n=554, SOC (HCQ/AZT/ Steroids/ HCQ+AZT)	n=210, TCZ-400mg-IV, Single-dose + SOC	60-day mortality	Nil	Multivariate Cox regression with propensity score
3	Campochiaro C *et al*., 2020 [33]	Retrospective Cohort	1) COVID-19 confirmed upon RT-PCR positivity for SARS-CoV-2. 2) elevation in either C-reactive protein (CRP, ≥100 mg/L) or ferritin (≥900 ng/mL), in the presence of increased lactate dehydrogenase (LDH, > 220 U/L); 3) severe respiratory radiological findings at chest x-ray and/or computed tomography (CT) scan 4) oxygen saturation (SaO2) ≤92%	n=65	n=33, SOC (HCQ -400 mg, OD daily +LPV/r/ RTV/r 400/100 mg BD + Ceftriaxone 2 gr for 6 days +AZT 500 mg daily + oxaparin 4000UI, SC OD)	n=32, TCZ-400mg, one/two IV dose	Mortality, the cumulative incidence of clinical, discharge from hospital, improvement, CRP, vitals. Time frame: Up to 30 days	Nil	Wilcoxon rank-sum tests for continuous variables and two-tailed Fisher's exact test for categorical variables. Kaplan-Meier survival analysis, log-rank test was used to compare survival curves
4	Canziani LM *et al*., 2020 [36]	Retrospective case-control	1) hospitalised patients with COVID-19 pneumonia 2) clinical worsening in the previous 24 h with an increasing need for oxygen or ventilatory support, 3) absence of clinical or biochemical signs of an active bacterial infection, 4) elevated C reactive protein, 5) A higher risk for mortality at blood tests.	n=128	n=64, SOC (enoxaparin, SC + LPV/r 400 mg + RTV/r 100 mg BD/DNV/r 800 mg + cobicistat 150 mg OD + HCQ 200 mg, BD)	n=64, TCZ- 8mg/kg, IV, one/two doses	Mortality, PaO2:FiO2, MV, IMV, Creatinine, D-dimer, Ferritin, Fibrinogen, Procalcitonin, LDH, IL-6, Hematology, INR, [Time Frame: up to 30 days]	Nil	Chi-square test and Mann-Whitney test were used according to the type of variable. Kaplan-Meier estimates were used for mortality analysis
5	Capra R *et al*., 2020 [21]	Retrospective observational study	1) COVID-19 confirmed upon RT-PCR, along with atleast one of the following conditions: 1) respiratory rate ≥30 breaths/min, 2) peripheral capillary oxygen saturation (SpO2) ≤93% while breathing room air, 3) PaO2/FiO2 <=300 mmHg	n=85	n=23, SOC (HCQ 400 mg daily and LPV/r 800 mg daily plus RTV/r 200 mg daily	n=62, Tocilizumab-400/324mg-IV/SC + SOC	Mortality, LOS, Clinical Improvement, No of discharges Time frame: up to 14 days	Nil	Kaplan-Meier survival analysis
6	Colaneri M *et al*., 2020 [39]	Retrospective	1) hospitalised patients with COVID-19 pneumonia	n=112	n=91, SOC (HCQ- 200 mg bid + AZT - 500 mg OD, LMWH ± methylprednisolone - 1 mg/kg up to 80 mg for 10 days)	n=21, TCZ - 8mg/kg IV, One/Two doses + SOC	Mortality, ICU Admission, INR, LDH, Lymphocytes, Neutrophils, ALT, CRP, procalcitonin, platelets, P/F ratio [Time Frame: day 0, Day 7]	Nil	Propensity Score Matching. Multiple imputations with predictive mean matching using the chained equation for missing data
7	De Rossi N *et al*., 2020 [41]	Retrospective cohort study	1) COVID-19 confirmed upon RT-PCR 2) bilateral pulmonary interstitial opacities on chest imaging 3) respiratory failure	n=158	n=68, SOC, (HCQ- 400 mg daily + LPV/r 800 mg + RTV/r 200 mg per day).	n=90, TCZ - 400 mg IV or 324 mg SC + SOC	Mortality, Vitals, CRP, Procalcitonin, Heamatology, LFTs, Creatinine-kinase, LDH, Coagulation Parameters The need for Respiratory Support.	Nil	Kaplan-Meier survival analysis

Sl. No	Author name	Study design	The population included in the study	Total no. of patients (Control + TCZ)	Control group	Tocilizumab (TCZ) Treatment	Parameters	Funding	Adjustments in The analysis (statistical analysis)
8	Gokhale Y *et al*., 2020 [31]	Retrospective Cohort	1) patients with severe COVID-19 pneumonia with lung infiltrates, elevated inflammatory markers and persistent hypoxia	n=161	n=91, SOC (antibiotics, HCQ 400 mg + Ivermectin 12 mg once daily, Oseltamivir 75 mg twice daily + LMVH 1 mg/ kg SC once daily + methylprednisolone 125 500 mg intravenously once daily)	n=70, TCZ-400 mg-IV along with SOC	Mortality, CRP. LOS, Ventilation. Time frame: up to 50 days	Nil	Multivariant Cox regression analysis
9	Guaraldi G *et al*., 2020 [28]	Retrospective, observational cohort study	1) adults ((≥18 years) with severe COVID-19 pneumonia	n=544	n=365, SOC (HCQ- 400 mg BD on D1, followed by 200 mg BD on days 2–5 ± AZT 500 mg OD for 5 days +LPV/r–RTV/r (400/100 mg BD/DNV/r–cobicistat (800/ 150 mg OD for 14 days + LMWH)	n=179, TCZ-162 mg, SC, n=88, TCZ - 8 mg/kg bodyweight, (Max 800mg)	Mortality, Incidence of MV, CRP, IL-6, D-dimers, Ferritin, Lymphocyte count, WBC. Time frame: up to 20 days	Nil	Adjusted for age, sex, recruiting centre, duration of symptoms, and Subsequent Organ Failure Assessment (SOFA) score, steroid use. Multivariate Cox regression analysis
10	Kewan T *et al*., 2020 [30]	Retrospective cohort study	1) hospitalised, adults ((≥18 years)with severe COVID-19	n=51	n=23, SOC (HCQ-400mg as loading dose b.i.d, followed by 200mg as maintainance dose b.i.d for 5 days)	n=28, TCZ-4-8mg/kg-IV+ prednisone-50mg	Mortality, LOS, LOS in ICU, Haematology, Clinical improvement, oxygen therapy, LFTs, CRP and IL-6, D-dimers, Fibrinogen, Ferritin, Creatinine, Troponin, vitals. Time frame: up to 30 days	Nil	Continuous variables were compared using the Wilcoxon-Mann-Whitney test. Categorical variables were compared using chi-squared or Fisher's exact test. Kaplan-Meier analysis and log rank test
11	Klopfenstein T *et al*., 2020[25]	Retrospective case-control study	1) COVID-19 confirmed upon RT-PCR	n= 45	n=25, SOC (HCQ or LPV/r – RTV/r therapy along with other antibiotics and CORTs)	n=20, TCZ - 400mg one/two doses IV + SOC	Mortality and/or ICU admission, MV, LOS, BP, Respiratory rate, Saturated O_2 (%), Lymphocytes, CRP, Duration of oxygen therapy (days), Time from symptom onset to TCZ initiation (days), [Time Frame: upto 24 days].	Nil	Continuous variables were compared by ANOVA test. Categorical variables were compared by chi-squared test or Fisher's exact
12	Martínez-Sanz J *et al*., 2020 [23]	Retrospective	1) hospitalised, Aadults ((≥18 years) with COVID-19 confirmed upon RT-PCR	n=1229	n=969, SOC (HCQ ± LPV/r /RTV/r ± AZT ± CORTs)	n=260, TCZ - 400-600 mg, in one/two doses, IV	Mortality, Non-ICU length of stay, ICU length of stay, Vitals, Differential count, LDH, ALT, Creatinine Urea, D-Dimer, IL-6, C-reactive protein, [Time Frame: up to 90 days]	Nil	Continuous variables were compared by ANOVA test. Categorial variables were compared by chi-squared test or Fisher's exact.
13	Mikulska M *et al*., 2020 [29]	Retrospective	1) adult patients admitted to the San Martino University Hospital, Genova, Italy, for COVID-19 pneumonia.	n=196	n=66, SOC (HCQ- 400mg bid ± DNV/r and/or /RTV/r 800/100 QID+ Antibiotics + LMWH)	n=130, TCZ - 8mg/kg (maximum 800mg), IV One/ two doses or TCZ 162 mg SC + methylprednisolone -1mg/kg for 5 days IV, then 0.5mg/kg	Mortality, IL-6, Ferritin, CRP, D-dimer, PaO2/ FiO2, non-invasive ventilation (NIV), [Time frame: up to 30 days]	Nil	Propensity score-based analysis followed by Cox regression analysis

Sl. No	Author name	Study design	The population included in the study	Total no. of patients (Control + TCZ)	Control group	Tocilizumab (TCZ) Treatment	Parameters	Funding	Adjustments in The analysis (statistical analysis)
14	Moreno-García E *et al*., 2020 [22]	Retrospective Cohort	1) patients with COVID-19 confirmed upon RT-PCR	n=171	n=94, SOC (LPV/r/RTV/r 400/100 mg BID for 7-14 days + HCQ 400 mg/12h on D1, followed by 200 mg/12h for the next 4 days + AZT 500 mg on day one followed by 250 mg/24h for next 4 days)	n=77, TCZ-400mg, one/ two/three IV doses + SOC	Mortality, Hospital discharge, Incidence of ICU stay, CRP, D-dimers, Ferritin, Lymphocyte count. Time frame: up to 30 days	Nil	Propensity score matching followed by multivariant analysis.
15	Moreno-Pérez O *et al*., 2020 [42]	Retrospective cohort study	1) patients with COVID-19 pneumonia	n=236	n=159, SOC (HCQ, LPV/r/ RTV/r, AZT)	n=77, TCZ initial 600 mg, with a second or third dose (400 mg), IV	Mortality, LDH, ALT, AST, LOS, LOS-ICU, PaO2: FiO2, Respiratory rate, BP, Heart rate, eGFR, Leukocytes, Lymphocytes, CRP, Procalcitonin, Ferritin, D-dimer, LDH, IL-6, Troponin T, Brain natriuretic peptide, Creatine phosphokinase, Time frame: up to 80 days	Nil	Categorical and continuous variables were compared by Mann-Whitney U-test, chi-squared test, and Fisher's exact tests. Followed by multivariant regression analysis
16	Pettit NN *et al*., 2020 [37]	Single-centre, retrospective, observational study	1) adult in-patients with COVID-19	n=148,	n=74, SOC (HCQ alone/HCQ +Ribavarin/ HCQ +LPV/r/Rtv/r)	n=74, TCZ + SOC ICU admission, mechanical ventilation, corticosteroids were avoided	Infection risk, CRP, ferritin, D-dimer. Time frame: up to 90 days	Nil	Student t-test and/or Mann-Whitney U-test.
17	Quartuccio L *et al*., 2020 [38]	Retrospective	1) patients with COVID-19 confirmed upon RT-PCR	n=111	n=69, SOC (Antivirals/ Glucocorticoids/ Antimalarials/ Antibiotics/ LMWH)	n=42, TCZ-8mg/kg, IV, single Dose + SOC	WBC count, differential count, $CD4^+$ T cells, $CD8^+$ T cells, $CD19^+$ B cells, $CD56^+$ NK cells, Platelet count, CRP, D-dimer, LDH, IL-6, Creatinine Kinase [Time frame Up to 30 Days]	Nil	Categorical variables were compared by Mann-Whitney test and continuous variables by t-test. Proportions were compared by Chi-squared test or Fisher exact test. Bivariate correlation was: performed by two-tailed Pearson or Spearman tests.
18	Ramaswamy M *et al*., 2020 [43]	Retrospective	1) hospitalised, adults ((≥18 years)with COVID-19 confirmed upon RT-PCR	n=86	n=65, SOC (AZT and/or HCQ and /or ACE inhibitors and/or CORTs)	n=21, TCZ - 8mg/kg IV, upto 800mg dose	AST, ALT, ASP. D-dimer, IL-6, CRP, Haematology, eGFR, INR, Ferritin, Procalcitonin, Serum Creatinine, BUN, Total bilirubin Time frame: up to 35 days	Nil	t-tests for continuous variables and Chi-squared test for binary and categorical variables. treatment effects models
19	Rojas-Marte G *et al*., 2020 [34]	Retrospective	1) adult patients hospitalised with severe to critical SARS-CoV-2 infection (COVID-19)	n=193	n=97, SOC (HCQ+RMV/r+ AZT+CORTs+ Vit C+ zinc)	n=96, TCZ + SOC	Mortality, LOS, Vitals, CRP, D-dimers, Ferritin, troponin, differential count, oxygen requirement, Procalcitonin. Time frame: up to 30 days	Nil	Student's t-test for continuous variables and the Chi-squared test or Fisher's exact test for categorical variables.
20	Rossi B *et al*., 2020 [19]	Retrospective case-control study, cohort	1) COVID-19 positive testing with RT-PCR) or chest CT-scan with typical lesions. 2) severe COVID-19 pneumonia	n=168	n=84, SOC (Antibiotics/ HCQ/ LPV/r or RTV/r/BCB/ Immunosupressants or CORTs)	n=84, TCZ-400mg single IV dose up to 30 days	Mortality, survival with MV, CRP, Lymphocytes. Time frame:	Nil	Propensity-score matching followed by Cox multivariable survival analysis

Sl. No	Author name	Study design	The population included in the study	Total no. of patients (Control + TCZ)	Control group	Tocilizumab (TCZ) Treatment	Parameters	Funding	Adjustments in The analysis (statistical analysis)
21	Roumier M *et al*., 2020 [24]	Retrospective	1) COVID-19 positive patients 2) age <80 years 3) severe rapidly deteriorating pneumonia, 4) high C-reactive protein levels and 5) with ≥5 days of prior disease duration.	n=59	n=29, SOC (HCQ -200MG t.i.d, AZT -250mg b.i.d and q.i.d day one onwards, Or > 1mg/kg b w of methyl prednisolone)	n=30, TCZ - 8mg/kg IV, One/Two doses + SOC (HCQ -200MG t.i.d, azithromycin -250mg b.i.d. and q.i.d after one day)	Mortality, MV, Incidence Of ICU, CRP, Ferritin, D-dimer, CT of Lungs, Time frame: up to 10 days	Nil	Inverse probability of treatment weighted methodology
22	Somers EC *et al*., 2020 [35]	Retrospective Cohort	1) COVID-19 positive testing with RT-PCR) 2) Require invasive mechanical ventilation.	n=154	n=76, SOC (HCQ/RMV/r+ Supportive Drugs)	n=78, TCZ-400mg, one/two IV dose	Mortality, Superinfection, discharged from hospital, LOS. Time frame: up to 30 days	Nil	Kaplan-Meier survival curves, Univariate and multivariable analysis.
23	Wadud N *et al*., 2020 [40]	Retrospective case-control study	1) COVID-19 positive testing with RT-PCR) 2) at least 18 years of age 3) admitted to the hospital between Mar 15, 2020, to Apr 20, 2020	n=94	n=50, SOC (HCQ, AZT, Steroids like hydrocortisone/ methylprednisolone/ dexamethasone)	n=44, TCZ + SOC (HCQ, AZT, Steroids like hydrocortisone/ methylprednisolone/ dexamethasone)	Mortality, CRP, IL-6, TGL, ferritin, fibrinogen, AST, D-dimer, fibrinogen, EKG,	Nil	Z score was calculated, and the mean value is compared between the two groups.
24	Zheng KL *et al*., 2020 [20]	Retrospective	1) COVID-19 positive testing with RT-PCR) with evidence of pneumonia	n=181	n=92, SOC (details are not available in the article, we have approached the authors to provide the details of conventional treatment mentioned in the manuscript, however there is no response from the authors)	n=89, TCZ-4-8mg/kg-IV + SOC	Mortality, discharge, LOS, hematology, LFTs, electrolytes, CRP, IL-6, D-dimers, Fibrinogen, Ferritin, Creatinine Kinase, Troponin T, Lactate Dehydrogenase, vitals. Time frame: up to 30 days	This work was supported by Shanghai Natural Science Foundation Grant no. 19ZR145580	For continuous variables, either unpaired t-tests or Mann-Whitney's U test was used. For multiple groups comparison, one-way ANOVA or Kruskal-Wallis test was used. Categorical variables were analysed using the chi-squared test or Fisher's exact test, as appropriate.

TCZ: tocilizumab; SOC: standard of care; LPV/r: lopinavir; RTV/r: ritonavir; BCB: Baricitinib; CORT: corticosteroids; HCQ: hydroxychloroquine; AZT: azithromycin; RMV/r: remdesivir; DNV/r: darunavir; IV: intravenous; SC: subcutaneous; MV: mechanical ventilation; IMV: invasive mechanical ventilation; ICU, intensive care unit; CRP: C-reactive protein; IL-6: interleukin-6; LFT: liver function tests, LOS: length of hospital stay; LOS-ICU: length of stay in the ICU; LMWH: low molecular weight heparin.

ratio (RE-OR) of 0.56 (0.38 to 0.84), at 95% CI, p=0.005, I^2=83%) compared to control/SOC. The effect of TCZ on COVID-19 induced mortality of depicted in Figure 2.

ICU ward admission rate

Six retrospectives studies involving 542 patients in the TCZ treatment and 1595 patients in the control/SOC, with a total of 2137 COVID-19 positive patients were considered for the analysis. The outcomes of the meta-analysis revealed that there is a statistically significant difference observed between the TCZ and control/SOC treatments in reducing the incidences of ICU ward admission rate (M-H, RE-OR of 0.91 (0.24–3.44) at 95% CI, p=0.89, I^2=94%). The results are given in Figure 3.

Need for mechanical ventilation

Twelve retrospectives studies involving 756 patients in the TCZ treatment and 1052 patients in the control/SOC, with a total of 1808 COVID-19 positive patients were considered for the analysis. The outcomes have revealed that there is no difference between the TCZ and control/SOC group in the terms of need for MV during the hospital stay (M-H, RE-OR of 1.11 (0.68–1.81) at 95% CI, p=0.69, I^2=63%). The forest plot analysis is depicted in Figure 4.

Effect of TCZ on length of hospital stay (LOS)

The LOS was evaluated by considering the eight retrospective studies comprising of a total of 2030 COVID-19 positive patients, of which 1395 (68.7%) patients were assigned to the TCZ treatment arm and 635 (31.2%) patients were into the control/SOC group. The results of the meta-analysis showed that there was substantial heterogeneity among the included studies (I^2=100%) and there was no statistically significant difference in LOS (days), observed between the TCZ and control/SOC groups (inverse variance (IV): -2.86 (-0.91–3.38) at 95% CI, p=0.37, I^2=100%). The forest plot analysis for LOS is depicted in Figure 5.

Effect of TCZ on length of hospital stay in ICU (LOS-ICU)

The LOS-ICU was analysed using three retrospective studies including a total of 1325 COVID-19 positive patients, of which 308 (23.2%) patients were assigned to the TCZ + SOC treatment arm and 1017 (76.8%) patients were into the control/SOC group. The results of the

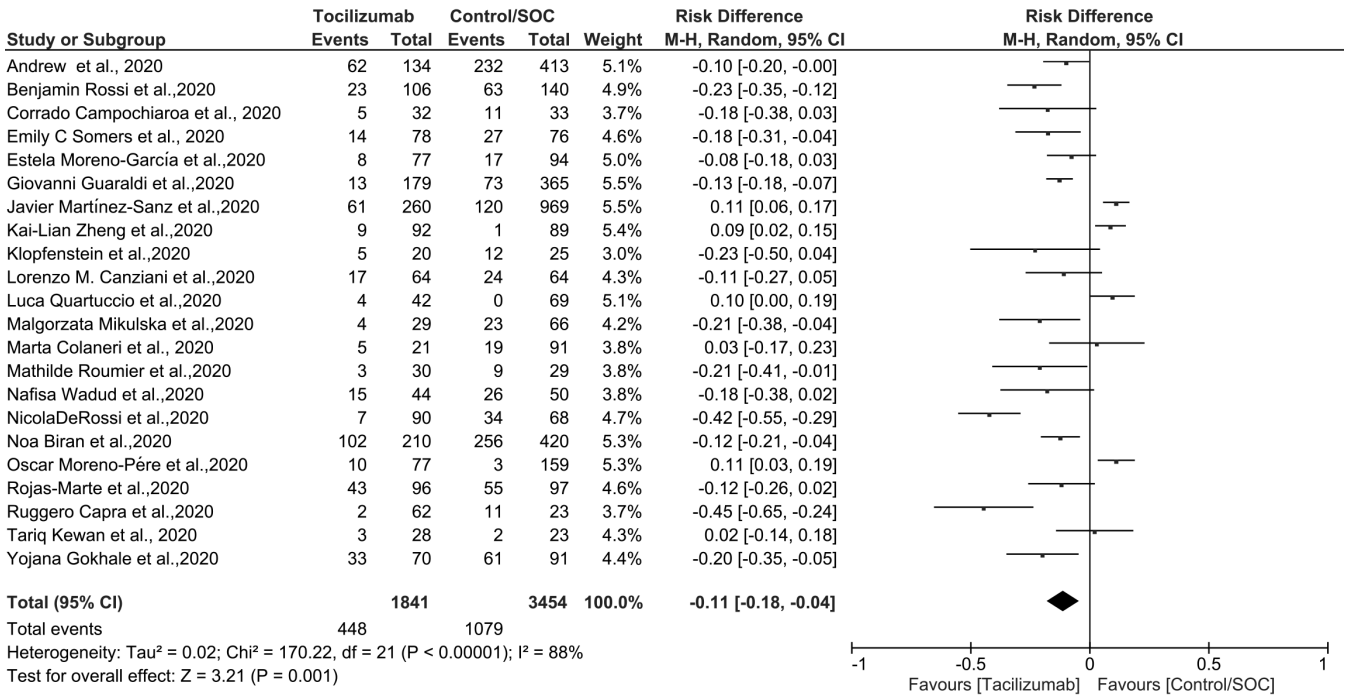

Fig. 2. Effect of tocilizumab on COVID-19 mortality.

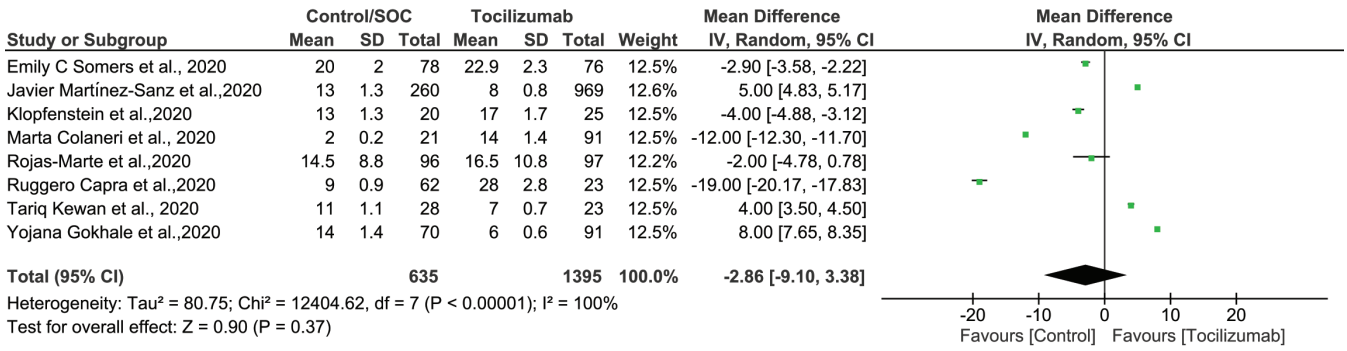

Fig. 3. Effect of tocilizumab on COVID-19 related ICU ward admission rate.

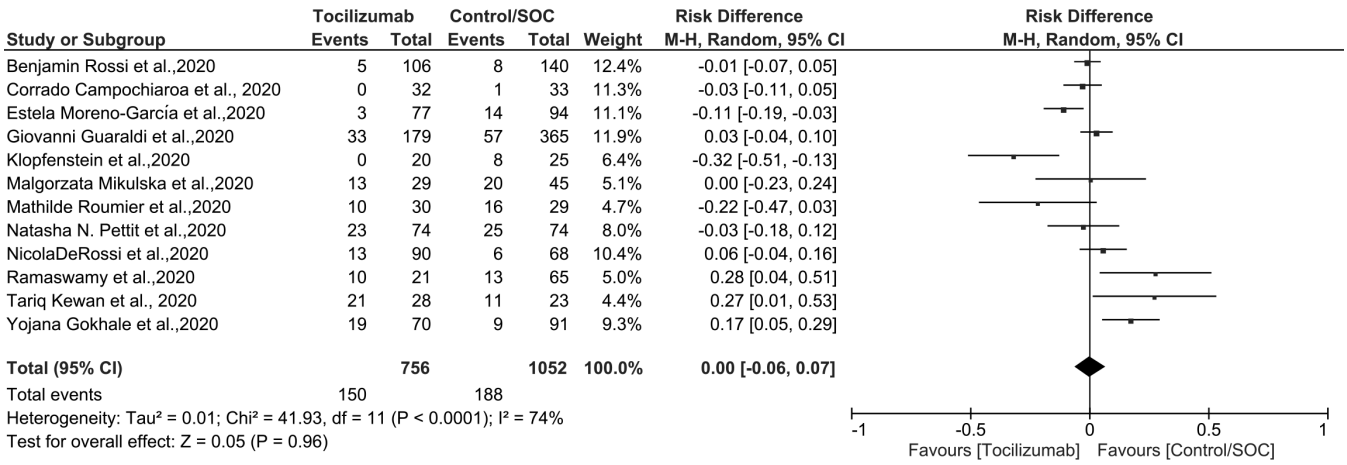

Fig. 4. Effect of tocilizumab on the need of mechanical ventilation in COVID-19 patients.

meta-analysis showed that there was substantial heterogeneity among the included studies (I^2=100%) and there was no statistically significant difference in LOS-ICU (days) observed between the TCZ and control/SOC groups (IV: -3.93 (-12.35–4.48) at 95% CI, p=0.36, I^2=100%). The forest plot analysis for LOS is depicted in Figure 6.

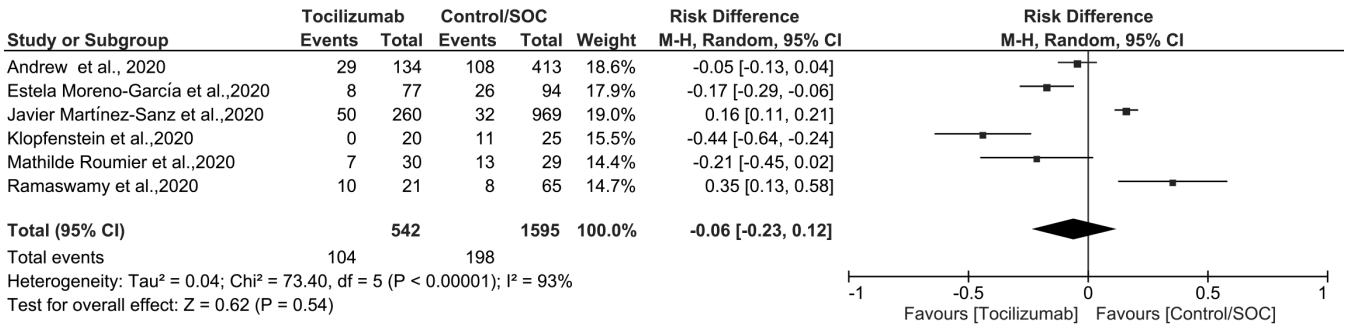

Fig. 5. Effect of tocilizumab on length of hospital stay (LOS) in COVID-19 patients.

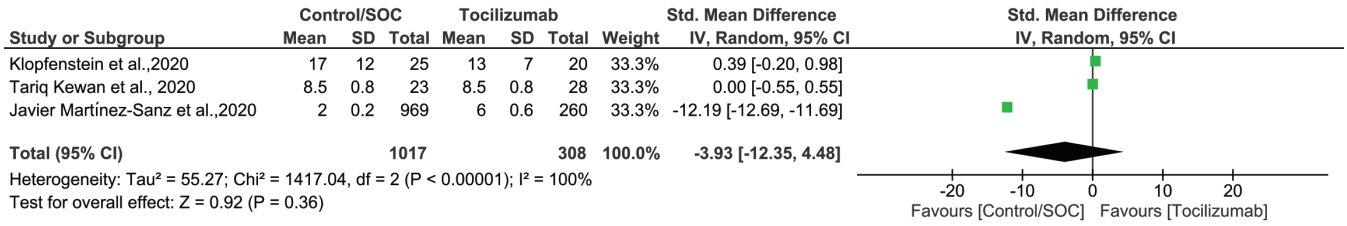

Fig. 6. Effect of tocilizumab on length of hospital stay in ICU (LOS-ICU) in COVID-19 patients.

Incidence of toclimuzab-induced infections

- Super-infections

The incidence of TCZ-induced super-infections was determined from the eight retrospective studies carried on 1,441 patients out of which 800 (55.5%) were under the control/SOC group and 641(44.4%) patients were considered under the TCZ group. The meta-analysis revealed that the chances of super-infections are slightly high in the TCZ treated group compared to control/SOC (M-H, RE-OR of 1.81 (1.08, 3.01) at 95% CI, p=0.02, I^2=60%), however, there is a significant heterogenicity among the studies included for the analysis.

- Fungaemia

The incidence of TCZ-induced fungaemia was determined from the three retrospective studies carried on 392 patients, out of which 194 (49.5%) were under the control group and 198(50.5%) patients were assigned under the TCZ group. The meta-analysis revealed that there is no statistically significant difference among the TCZ and control/SOC groups observed in the incidences of fungaemia (M-H, RE-OR of 1.73 (0.51, 5.87) at 95% CI, p=0.38, I^2=0%).

- Bacteraemia

The incidence of TCZ-induced bacteraemia was determined from the four retrospective studies carried in 956 patients, out of which 571 (59.3%) patients were under the control/SOC group and 385 (40.2%) patients were assigned under the TCZ group. The outcomes of the meta-analysis showed no difference among the TCZ and control/SOC groups, in the incidences of bacteraemia (M-H, RE-OR of 0.92 (0.46, 1.82) at 95% CI, p=0.80, I^2=35%).

- Pneumonia

This parameter was analysed by considering the four retrospective studies carried on 897 patients, out of which 538 (60%) were under the control group and 359(40%) patients were assigned into the TCZ group. The outcomes of the analysis revealed that TCZ treated group has more chances of pneumonia compared to the control/SOC group (M-H, RE-OR of 2.44 (1.50, 3.96) at 95% CI, p=0.0003, I^2=0%).The forest plot analyses of the incidence of TCZ-induced infections are depicted in Figure 7.

Incidence of toclimuzab-induced pulmonary thrombosis

The incidence of pulmonary thrombosis was determined from the two retrospective studies carried on 193 patients, of which 97 (50.3%) patients were under the control/SOC group and 96(49.7%) patients were assigned under the TCZ group (received at least one dose of TCZ). The outcomes of the analysis revealed that there was no significant difference in the incidences of pulmonary thrombosis between TCZ and control/SOC treated groups (M-H, fixed effect odds ratio (RE-OR) of 1.01 (0.45–2.27) at 95% CI, p=0.98, I^2 = 0%). The forest plot analysis of the incidence of TCZ-induced pulmonary thrombosis is depicted in Figure 8.

Discussion

This systematic review and meta-analysis were performed to collect, analyse, interpret and conclude the efficacy and safety of TCZ in the treatment of COVID-19 positive subjects. Since the emergence of the pandemic, globally the scientists are in search of a medicine or treatment strategy to combat or manage the pandemic and thereby reduce the social-economic burden throughout the world (17). Many multi-national organisations, research organisations, and academic researchers are extensively working on developing an effective treatment for COVID-19 (18). As of now, it has been symptomatically managed by using already existing medications such as antivirals (remdesivir, oseltamivir, etc.), anti-pyretic (paracetamol), anti-histaminic (cetirizine,), antibiotics (cephalosporins), corticosteroids (prednisolone, methylprednisolone), monoclonal antibodies (tocilizumab, imatinib) (19).

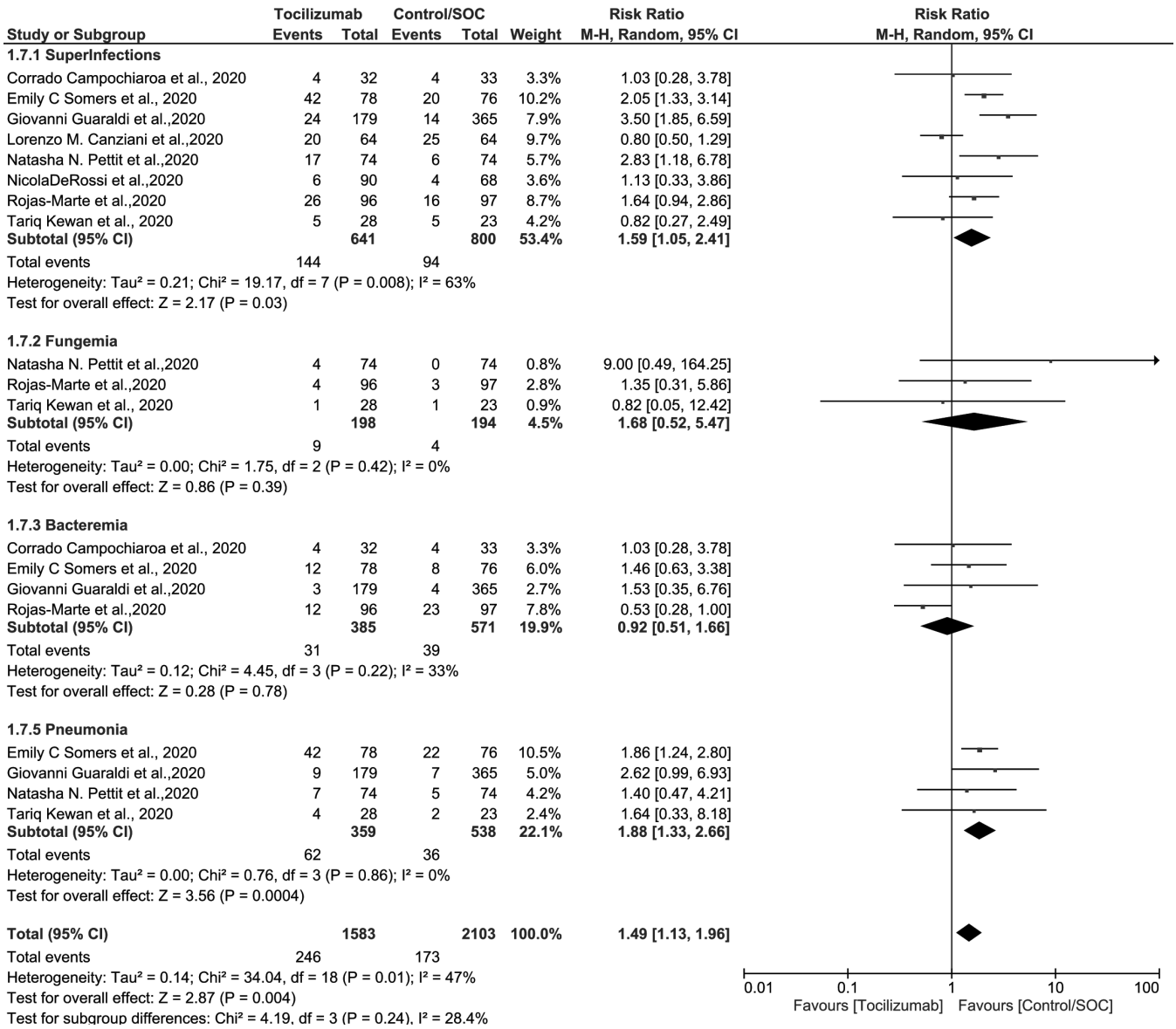

Fig. 7. The incidences of toclimuzab-induced super-infections in COVID-19 patients.

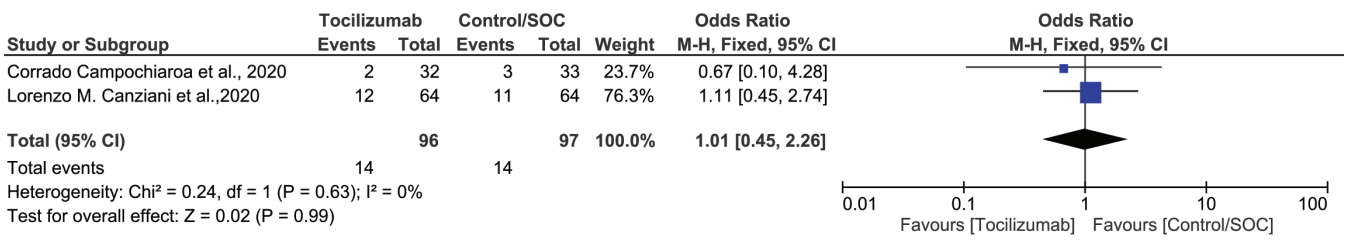

Fig. 8. The incidents of toclimuzab-induced pulmonary thrombosis in COVID-19 patients.

In this context, the IL-6 antagonists are considered to have better therapeutic benefits in the symptomatic management of COVID-19, in these lines, TCZ is considered as one of the most commonly used medication to suppress the cytokine storm in COVID-19 patients (20). There are multiple case series, retrospective, and prospective studies available on the therapeutic role of TCZ in COVID-19. Also, there are few meta-analysis reports published related to the therapeutic use of TCZ in COVID-19. However, this study was focused to provide an overall view on the efficacy and safety of TCZ in COVID-19 patients considering the retrospective studies/reports available on the topic till October 2020.

Based on the inclusion and exclusion criteria a total of 24 retrospective studies were selected for this study, comprising of 5686 COVID-19 positive patients. The parameters such as mor-

tality, ICU ward admission rate, need for MV, length of hospital stay, length of hospital stay in ICU, Incidence of super-infections such as fungaemia, bacteraemia, pneumonia, and pulmonary thrombosis were considered for systematic review and meta-analysis.

The available literature favours the benefit of TCZ in minimising the COVID-19 induced mortality (21-24). In this study, 22 included studies have reported mortality as a parameter of which 16 studies have supported the use of TCZ in minimising the mortality, and 6 studies have shown results in favour of control. The outcome of the meta-analysis revealed that the administration of TCZ could benefit the COVID-19 positive patients in minimising the COVID-19 induced mortality.

Further, among the hospitalised COVID-19 positive patients about 5-10% population requires ICU admission (25, 26). In this regard, some of the available reports have supported the use of TCZ in reducing the incidences of ICU admission (25-27). However, the outcomes of the present meta-analysis showed that there is no significant difference between the TCZ and control/SOC groups in the incidences of ICU admission among the COVID-19 infected patients.

Moreover, about 89.9% of ICU cases and 20.2% of hospitalised COVID-19 positive patients require MV (invasive and/or non-invasive) (29), and the role of TCZ in reducing the need for MV has been evaluated in multiple studies (30-34). In the present study, 12 retrospective studies reporting the MV as a parameter were included, of these 12 studies, 7 studies have reported in favour of TCZ, 5 studies have reported in favour of control/SOC and 1 study was neutral. The outcomes of the meta-analysis revealed that the need for MV is the same between TCZ and control/SOC treated groups.

Besides, length of stay (LOS and LOS-ICU) is the one of important parameters considered for evaluating the efficacy in COVID-19 patients. As per the available data, the median LOS was found to be 4 to 21 days (outside China) and median LOS-ICU was found to be 4 to 19 days (outside China) (35). In this regard, 8 studies reporting LOS and 3 studies reporting LOS-ICU were included in the present study. On the overview, the TCZ treatment has shown benefit in minimising the LOS and LOZ-ICU compared to control/SOC. However, there was no statistically significant difference observed between the TCZ and control/SOC groups, due to the significant heterogenicity (I^2=100%) associated with the included studies.

On the other hand, the safety of TCZ is the prime concern while administering to COVDI-19 patients. The available literature suggests that TCZ administration can cause adverse (AEs) and serious adverse events (SAEs) such as super-infections, fungaemia, bacteraemia, pneumonia, pulmonary thrombosis, and so on (36-41). Therefore, the incidences of events such as these adverse events were compared between the TCZ and control/SOC treated groups using the 9 included studies. The outcomes of the meta-analysis revealed that the TCZ administration has higher chances of producing the events such as super-infections, fungaemia, bacteraemia, pneumonia, and pulmonary thrombosis compared to control/SOC.

Further, we found that there are 7 systematic reviews and meta-analyses published based on observational studies on the role of tocilizumab in the treatment of COVID-19 (48-54). However, a meta-analysis published by Aziz *et al*. (48) has a close association with this meta-analysis. Aziz *et al*. included 23 studies involving 6279 patients, and the parameters such as mortality, need for MV, ICU admission, and secondary infections were considered as parameters (48). However, we have included additional parameters such a LOS, LOS-ICU, role of TCZ treatment on incidences of super-infections, and also evaluated the incidences of TCZ-induced pulmonary thrombosis. In addition, our analysis has a greater number of studies in the parameters like mortality and the need for MV. Lastly, in the conclusion section Aziz *et al*. have stated that TCZ treatment has the potential to decrease the mortality rate in severe COVID-19 patients without causing a significant increase in the infection rate (48).

Commenting on other meta-analysis works, Zhao *et al*. have performed a meta-analysis including 10 studies, comprising 1675 patients. Mortality, admission to ICU, safety, and efficacy were considered for analysis. This study has concluded that TCZ treatment could reduce mortality significantly compared to control/SOC in severe COVID-19 patients (49). Further, the meta-analysis performed by Liu *et. al*. has included 28 studies consisting of 991 COVID-19 confirmed patients receiving TCZ. They have concluded that TCZ administration has reduced the death rate in severe COVID-19 cases (50). Moreover, Surjit Singh *et al*. have performed a meta-analysis including a total of 13 observational studies comprising 2750 patients. Based on the detailed analysis they have concluded that there is a 46% decrease in mortality rate, and a 66% decrease in the progression of diseases in TCZ treated group compared to the SOC group (51). Besides, based on the meta-analysis of 16 studies Boregowda *et al*. have concluded that the addition of TCZ to the standard regimen could reduce the mortality in severe COVID-19 patients (52). On the other hand, Kotak S *et al*. have carried a meta-analysis including 13 studies consists of a total of 766 patients. Based on the observations, authors have concluded that TCZ is safe and effective in reducing mortality among critically ill COVID-19 patients. However, this study has very limited numbers of observations. However, a systematic review made by Lan *et al*. has concluded that the available pieces of evidence are not strong enough to derive a conclusive decision about the benefit of TCZ in treating COVID-19 and associated health complications. They have included 7 retrospective studies comprising of 592 adult COVID-19 patients (54).

Basides, there is a meta-analysis work published by Tleyjeh *et al*., wherein authors have included five RCTs of tocilizumab related to its benefits in COVID-19. The outcomes of the meta-analysis (based on RCTs) concludes that TCZ did not reduce the short-term mortality, and cumulative evidences suggest that there is a reduction in risk of MV. While, there was difference in

the risk of infections or adverse events between the TCZ and SOC groups (55). The pooled estimated of meta-analysis of RCTs Overall, based on the meta-analysis of moderately-certain evidence we can conclude that the administration of TCZ would reduce the risk of mortality, and however, there is no much difference observed between the TCZ and SOC/control groups in other parameters such as ICU admission rate, need for MV and length of hospital stay (ICU and non-ICU). On the other hand, TCZ treated subjects possess higher chances of adverse events like super-infections, fungaemia, bacteraemia, pneumonia, and pulmonary thrombosis compared to the control/SOC group.

Conclusions

This meta-analysis was performed using retrospective clinical reports on the use of TCZ in COVID-19, and based on the outcomes of the meta-analysis we can conclude that administration of TCZ would reduce the risk of mortality, and however, there is no much difference observed between the TCZ and SOC/control groups in other parameters such as ICU admission rate, need for MV and length of hospital stay (ICU and non-ICU). On the other hand, TCZ treated subjects possess higher chances of super-infections and pneumonia compared with SOC/control group. All the included studies have passed the quality assessment and showed a low risk of bias. However, the major limitation of this study is the significant heterogenicity observed in the outcomes due to multiple confounding factors, and hence there is a need for multi-centric randomised trials involving a large COVID-19 patient population, proper adjustment of confounders like SOC medications to determine the potential therapeutic role of TCZ in mitigating COVID-19 and associated health complications.

Limitations

Our meta-analysis has many limitations. Firstly, all the included articles are observational studies and the observational studies are not as robust as randomised controlled studies. Secodnly, there was a moderate to significant heterogenicity observed in the outcomes of the various parameters evaluated. Interestingly, the observed heterogenicity between the included studies is due to multiple reasons as highlighted below. All the included studies are observational, and the confounders associated with one or two included studies may also influence the outcomes to a large extent. Besides, since there was no specific treatment available for COVID-19 (before the approval of vaccine), the therapies are dynamically evolving with each passing day, therefore the comparator group or standard of care (SOC) or control group has varied significantly from study to study, this is also one of the potential causes for heterogenicity observed. Lastly, there was no standard treatment regimen available for tocilizumab use in the included studies, like there is the difference in dosage regimen (strength and number of doses), route of administration, time of administration, age, and gender difference. These are some of the possible reasons for significant heterogenicity observed in the outcomes of the present study.

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