**ΠΑΝΕΠΙΣΤΗΜΙΟ ΘΕΣΣΑΛΙΑΣ**
**ΤΜΗΜΑ ΙΑΤΡΙΚΗΣ**

ΠΜΣ «Μεθοδολογία Βιοϊατρικής Έρευνας, Βιοστατιστική
και Κλινική Βιοπληροφορική

**ΜΕΤΑΠΤΥΧΙΑΚΗ ΔΙΠΛΩΜΑΤΙΚΗ ΕΡΓΑΣΙΑ**

**ΤΙΤΛΟΣ**

«Αξιολόγηση της ποιότητας αναφοράς τυχαιοποιημένων κλινικών δοκιμών που αφορούν την χορήγηση *tocilizumab* σε ασθενείς που νοσηλεύονται με Covid-19, δημοσιευμένων από το 2020 έως το 2021, με βάση τη δήλωση CONSORT»

**TITLE**

"Assess the reporting quality of RCTs for *tocilizumab* in hospitalized covid-19 patients published from 2020 to 2021 using the CONSORT statement"

**ΤΡΙΜΕΛΗΣ ΣΥΜΒΟΥΛΕΥΤΙΚΗ ΕΠΙΤΡΟΠΗ:**
Ι. ΣΤΕΦΑΝΙΔΗΣ, Χ. ΔΟΞΑΝΗ, Η. ΖΙΝΤΖΑΡΑΣ

**ΜΕΤΑΠΤΥΧΙΑΚΗ ΦΟΙΤΗΤΡΙΑ: ΣΑΚΑΓΙΑΝΝΗ ΑΙΚΑΤΕΡΙΝΗ**

**ΛΑΡΙΣΑ, 2021**

**TABLE OF CONTENTS**

## Α. Περίληψη

**Εισαγωγή**: Από την αρχή της πανδημίας Covid-19, αρκετές τυχαιοποιημένες κλινικές δοκιμές (ΤΚΔ) που εξετάζουν την αποτελεσματικότητα του tocilizumab σε νοσηλευόμενους ασθενείς με Covid-19, έχουν δημοσιευτεί με αντικρουόμενα αποτελέσματα. Η αναφορά της ποιότητας των RCTs είναι καίριας σημασίας για την εξαγωγή ασφαλών συμπερασμάτων.

**Στόχοι**: Κύριος στόχος της μελέτης είναι να αξιολογήσει την ποιότητα αναφοράς των τυχαιοποιημένων κλινικών δοκιμών που αφορούν την αποτελεσματικότητα της χορήγησης τοσιλιζουμάμπης σε ασθενείς που νοσηλεύονται με Covid-19, δημοσιευμένων από το 2020 έως το 2021, με βάση τη δήλωση CONSORT.

**Μέθοδοι**: Αναζητήσαμε στο Pubmed όλες τις σχετικές αναφορές στην αγγλική γλώσσα. Κάθε κατάλληλη αναφορά εξετάστηκε για τη συμμόρφωσή της με την λίστα 37 στοιχείων της δήλωσης CONSORT. Η ταξινόμηση έγινε με βάση τον συντελεστή απήχησης του περιοδικού δημοσίευσης στο Journal Citation Reports™ (JCR).

**Αποτελέσματα**: Δώδεκα μελέτες βρέθηκαν κατάλληλες για αξιολόγηση. Η συνολική μέση βαθμολογία συμμόρφωσης CONSORT ήταν 68% (SD 16,51), με διάμεση τιμή 73% (IQR 29,05). Έξι δοκιμές (50%) κάλυψαν τουλάχιστον 75% των στοιχείων CONSORT, ενώ υπήρχαν τρεις ΤΚΔ (25%) με συμμόρφωση κάτω του 50%. Οι δοκιμές που δημοσιεύθηκαν σε περιοδικά υψηλότερης απήχησης παρουσίασαν στατιστικά σημαντική μεγαλύτερη συμμόρφωση με τη δήλωση CONSORT ($p<0,05$).

**Συμπέρασμα**: Η ποιότητα αναφοράς των ΤΚΔ που εξετάζουν την χορήγηση τοσιλιζουμάμπης σε ασθενείς με Covid-19 θεωρείται μέτρια. Η αναφορά της μεθοδολογίας, ιδίως ο υπολογισμός του μεγέθους του δείγματος, η απόκρυψη κατανομής και η εφαρμογή θα μπορούσαν να βελτιωθούν περαιτέρω.

**Λέξεις κλειδιά**: Covid-19, τοσιλιζουμάμπη, τυχαιοποιημένες κλινικές δοκιμές, CONSORT

**ABSTRACT**

**BACKGROUND**: Since the beginning of Covid-19 pandemic, several Randomized Controlled Trials (RCTs) examining the efficacy of tocilizumab in hospitalized Covid-19 patients, have been published with conflicting results. Reporting quality of RCTs is crucial for extracting safe conclusions.

**OBJECTIVES**: The main objective of this study is to assess the reporting quality of RCTs examining the efficacy of tocilizumab in hospitalized covid-19 patients, published from 2020 until 2021 based on the consolidated standards of reporting trials (CONSORT) statement.

**METHODS**: We searched Pubmed for all the relevant english-language RCTs. Each eligible reference was examined for its adherence to the 37-item list of CONSORT Statement. All the eligible RCTs were ranked according to the Journal Citation Reports™ (JCR) of the article's hosting Journal and the associated impact factor (IF).

**RESULTS**: Twelve studies were found eligible for assessment. The overall CONSORT compliance score had a mean value of 68% (SD 16,51), and a median value of 73% (IQR 29,05). Six trials (50%) covered at least 75% of the CONSORT items, while three RCTs (25%) had adherence less than 50%. Trials published in higher-ranked journals presented a statistically significant greater compliance with CONSORT statement ($p<0,05$).

**CONCLUSION**: The reporting quality of RCTs examining the efficacy of tocilizumab in Covid-19 patients is moderate. Methodology reporting, especially sample size calculation, allocation concealment and implementation issues could be further improved.

**Key words**: Covid-19, tocilizumab, Randomized Controlled Trials, CONSORT

## B. INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a respiratory disease induced by a novel coronavirus (severe acute respiratory syndrome corona virus 2 [SARS-CoV-2]) causing significant morbidity and mortality. Although most people with COVID-19 have only mild symptoms, approximately 10% to 15% have moderate or severe disease that requires hospitalization and oxygen support, while 3% to 5% require admission to an intensive care unit (ICU). In severe cases, COVID-19 can be complicated by acute respiratory distress syndrome (ARDS). Respiratory and multi-organ failure, are the leading causes of death in patients with COVID-19.

Patients with severe COVID-19 pneumonia present nonspecific inflammatory responses, including edema and inflammatory cell infiltration in the lungs. Besides the specific pathogenic effect of SARS-CoV-2, this deleterious excessive and non-effective host immune response plays an important role during the disease course. It is related to a hyperinflammatory status comprising a number of proinflammatory cytokines and chemokines, one of the most predominant being interleukin 6 (IL-6). A number of immunomodulatory therapies targeting these cytokines have recently gathered interest and have been tested in COVID-19.

Tocilizumab (TCZ) is an anti–interleukin-6 receptor (IL-6R) monoclonal antibody that inhibits IL-6 signaling by binding soluble IL-6R and membrane IL-6R and is currently approved for rheumatoid arthritis, juvenile inflammatory arthritis and refractory giant cell arteritis. Tocilizumab is also approved for systemic inflammatory response caused by the massive release of proinflammatory cytokines in response to iatrogenic disease (eg, chimeric antigen receptor T-cell therapies). These observations formed the basis for targeting IL-6 as a therapeutic approach for severe COVID-19 disease. Several studies, observational and randomized, addressing the therapeutic role of tocilizumab in COVID-19 patients have been published during the pandemic with conflicting results.

Randomized controlled trials provide the best evidence on the efficacy of medical interventions, when properly designed and performed. Random allocation to interventions is the only method that minimizes selection and confounding biases. Nevertheless, even a well-designed and executed clinical trial, should also be clearly and meticulously reported in order to avoid speculations made by the readers. Moreover, transparent reporting of methodology and results enables readers to critically appraise and interpret RCTs.

The Consolidated Standards of Reporting Trials (CONSORT) 2010 statement consists of a 37-item checklist and a flow diagram that guides authors in complete and accurate RCT reporting. Since its first publication in 1996, it has been endorsed by hundreds of well-known international journals and has been associated with improved reporting of randomized trials over time.

Aim of this study is to assess the reporting quality of randomized controlled trials (RCTs) concerning the efficacy of the IL-6 receptor antagonist tocilizumab in hospitalized COVID-19 patients, published from 2020 to 2021, using the Consolidated Standards of Reporting Trials (CONSORT) 2010 statement.

## C. **METHODS**

### ***Search method***

We searched Pubmed for all relevant RCTs that investigate the efficacy and safety of tocilizumab in hospitalized Covid-19 patients, published from 2020 until 2021. Each eligible trial was examined for its adherence to the 37-item list of CONSORT Statement. As a search criterion the following terms were used: "tocilizumab" and "covid-19". The following filters were used: "*Randomized Controlled Trials*", "*English*" language and "*Humans*" for species.

### ***Eligibility criteria***

Trials were eligible if they examined patients hospitalized with Covid-19 randomly assigned to at least two treatment arms, and included one intervention group that received tocilizumab, and a control group, or another comparator.

Reviews, systematic reviews, meta-analyses, non-randomized studies, observational studies, retrospective studies, cohort studies, conference abstracts, study protocols and editorials, were excluded.

### ***Data extraction***

The 2010 revised CONSORT statement (http://www.consort-statement.org/) was used to assess the reporting quality of the eligible trials. The CONSORT Explanation and Elaboration document was used in conjunction with the statement, as it is recommended. Data extraction was made by the author of this study. Each of the 37 items of the checklist was rated by 1 point, when adequately reported, 0 when either inadequately reported or absent. Regarding certain items, e.g 3b (changes to

methods), 6b (changes to trial outcomes), 7b (interim analyses and stopping guidelines), 11b (description of the similarity of interventions), 12b (subgroup analyses and adjusted analyses), 14b (why the trial ended or was stopped), 18 (ancillary analyses), when not relevant, they were checked as 'non applicable'. Reporting of an item in a different section of the article (title, abstract, introduction, methods, results, and discussion) was rated by 1. Reporting of an item in the appendix of a study was also positively appraised, provided there was a relevant reference inside the text. This rule was not applied to item 8a, where the CONSORT Explanation and Elaboration Document clearly denotes that "*information on the process of randomization is included in the body of the main article and not as a separate supplementary file; where it can be missed by the reader*." After the completion of the evaluation, the sum of the values for each RCT was extracted. The maximum possible score for an RCT report was 37. The scores were then converted to a percentage. After the evaluation of all studies, the total score of each item and the corresponding percentage were calculated by adding the item values for all trials.

***Statistical analysis***

All the eligible RCTs were ranked according to the Journal Citation Reports™ (JCR) (https://clarivate.com/webofsciencegroup/solutions/journal-citation-reports/) of the article's hosting Journal and the associated impact factor (IF) for 2020. We assumed that an article published in a higher ranked medical journal would present a closer adherence to the CONSORT statement, compared to a lower ranked one. In order to compare the compliance to the CONSORT statement we classified the eligible RCTs into two groups. We compared RCTs published in medical journals with IF $\geq$ 30 with those published in journals with IF < 10. The average compliance score between the two groups was compared using the non-parametric independent sample Mann-Whitney U test, after checking for normality with the Shapiro-Wilk's test. The statistical analysis was made on the IBM SPSS version 26 package. The cutoff point for statistical significance was set at the two-sided 0.05 level. A compliance score with the CONSORT statement $\geq$ 75% was considered an adequate reporting cut-off, in accordance with previous studies.

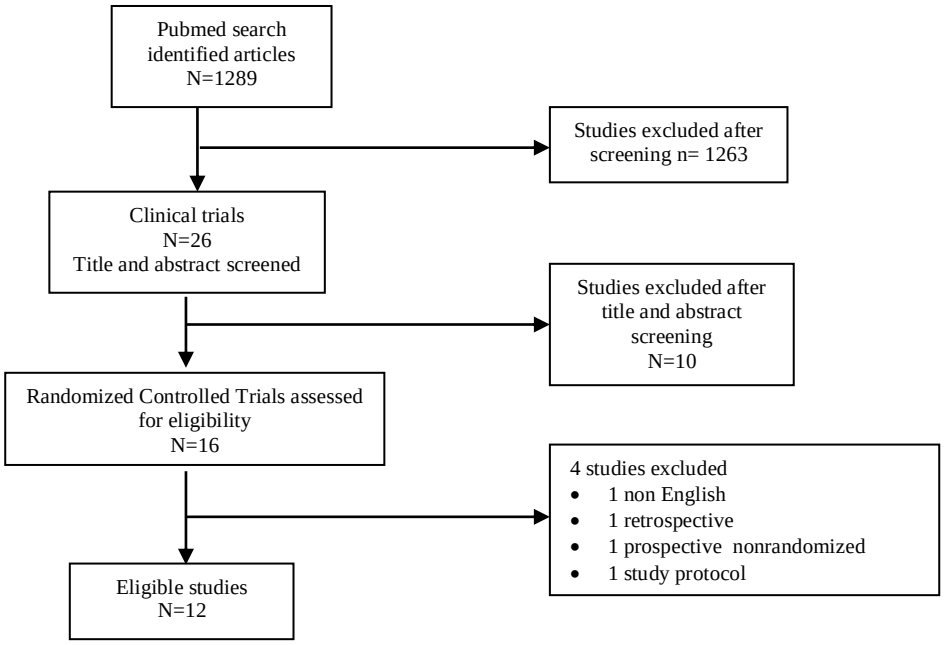


**Fig.1:** Flow diagram of the screening process

## D. RESULTS

Initial search in Pubmed under the terms "tocilizumab" and "covid-19" retrieved 1.289 results. A more restricted search yielded 26 clinical trials. Among them, there were 16 randomized controlled trials. One trial written in Russian language was excluded. Two trials were also excluded following assessment of the abstract, as their design was other than randomized (one retrospective, one non-randomized). One published protocol of a randomized trial was also excluded. A flow diagram of the screening process is shown in **figure 1**. Finally, 12 studies were found eligible for assessment. A list of these 12 RCTs, which included a total of 2834 randomized patients, can be found in the Appendix. All studies were conducted and published from 2020 to 2021, during the Covid-19 pandemic. Nine out of 12 studies (75%) were multicenter. Two thirds of the studies (75%) were open label and only three (25%) were double-blind, placebo controlled.

**Table 1:** List of the eligible trials, date of publication, Journal, Impact factor (2020) and CONSORT adherence score (%)

| Study | Month/Year | Journal | IF (2020) | Number of Patients randomized | CONSORT score (%) |
|---|---|---|---|---|---|
| Stone JH, et al.* | Dec 2020 | *N Engl J Med.* | 91,2 | 243 | 26/37 (70,3%) |
| Salama C, et al.* | Jan 2021 | *N Engl J Med.* | 91,2 | 389 | 26/37 (70,3%) |
| Rosas IO, et al. * | Apr 2021 | *N Engl J Med.* | 91,2 | 452 | 31/37 (83,8%) |
| REMAP-CAP Investigators¶ | Apr 2021 | *N Engl J Med.* | 91,2 | 895 | 30/37 (81%) |
| Salvarani C, et al.¶ | Jan 2021 | *JAMA Intern Med.* | 56,3 | 126 | 29/37 (78,4%) |
| Hermine O, et al. ¶ | Jan 2021 | *JAMA Intern Med.* | 56,3 | 131 | 32/37 (86,5%) |
| Veiga VC, et al. ¶ | Jan 2021 | *BMJ.* | 39,8 | 129 | 28/37 (75,7%) |
| Soin AS, et al. ¶ | May 2021 | *Lancet Respir Med.* | 30,7 | 180 | 28/37 (75,7%) |
| Zhao H, et al. ¶§ | Jan 2021 | *Biomed Pharmacother.* | 6,5 | 26 | 15/37 (40,5%) |
| Wang D, et al. ¶ | Jun 2021 | *Front Med.* | 4,4 | 65 | 25/37 (67,5%) |
| Rashad A, et al. ¶§ | Apr 2021 | *Sci Rep.* | 4,3 | 149 | 17/37 (45,9%) |
| Hamed DM, et al. ¶§ | Aug 2021 | *J Infect Public Health.* | 3,7 | 49 | 15/37 (40,5%) |

*Double-blind, placebo-controlled study. ¶Open-label study. §Single center study.

Eight different scientific journals hosted the included articles (Table 1). Three of them (JAMA, BMJ, NEJM) are currently CONSORT-endorsing, corresponding to 58% (7/12) of the articles. One third of the studies (4/12) were published in NEJM, the journal with the highest IF. According to the IF (JCR) of the hosting journals the eligible studies were classified into two groups. Eight out of the twelve RCTs (8/12)

that were used in the analysis, were published in high ranked medical journals (IF ≥ 30) and four (4/12) in lower ranked medical journals (IF < 10). The two groups of the articles presented a mean CONSORT adherence of 77,71% (SD 5,89) and 48,6% (SD 12,85), respectively. The respective median values were 77,05 (IQR 11,45) and 43,2 (IQR 21,60). A statistically significant greater compliance of articles published in higher ranked journals was observed, with p=0,004.

The overall CONSORT compliance score had a mean value of 68% (SD 16,51), and a median value of 73% (IQR 29,05). Six trials (50%) covered more than 75% of the CONSORT items, while there were only 3 RCTs (25%) with CONSORT compliance less than 50%.

Adherence per consort item was also evaluated. The word "randomized" was used in the **title** (item 1a) in only 5 trials (41,7%), while item 1b (abstract) was properly constructed and written in 10/12 studies (83,3%). **Introduction** (items 2a and 2b) provides adequate information about trial objectives and hypotheses in all the assessed RCTs (100%).

In **methodology** section, items regarding trial design (3a), participants (4a and 4b), and outcomes (6a) were assessed as adequately reported in most of the eligible trials. In only one RCT (Rosas et al), allocation ratio was not clearly reported probably due to the 'adaptive' design of the trial. In more than half of the studies (58%) authors have adequately described the interventions (item 5) and the sample size calculation (item 7a). Items 3b, 6b and 7b were probably not applicable in most of the studies, but this should be stated in the text. **Randomization** and allocation concealment were adequately reported. Sequence generation (item 8a) was sufficiently reported in 83% of the studies, randomization process (item 8b) and allocation concealment (item 9) were reported in 7/12 studies (58,3%), whereas implementation (item 10) in one-third (33,3%) of the studies. Reporting of who was blinded or aware after assignment to interventions (item 11a) was apparent in 5 studies (41,7%) and similarity of interventions (11b) was described in only two studies (16,7%) in the supplementary material. **Statistical methods** used to compare groups for primary and secondary outcomes (item 12a) were reported in 100% of the trials. On the contrary, methods for additional analyses were clearly specified in half of the RCTs (50%).

In the **results** section, a high compliance rate (above 80%), was observed in most of the examined fields, with adequate information documenting the flow of

participants through each stage of the randomised trials (13a, 13b), the periods of recruitment and follow-up (14a), baseline characteristics (15), and estimated effect size and its precision (17a). Underreporting was remarked in items 14b, 17b and 18 with compliance rates 33,3%, 16,7% and 41,7%, respectively. Safety data (item 19) are also properly reported in 83,3% of the RCTs.

In the **discussion** section, external validity or applicability issues (item 21) were commented in only 2 out of 12 studies (16,7%), whereas limitations (item 20) and interpretation (item 22) were reported in most of the studies. **Information** about where the full trial protocol can be accessed is given in 75% of the studies and registration number is reported in 91,7%. The level of involvement by a funder was stated by the authors in a substantial percentage (83%) of the assessed trials.

In 21 out of the 37 items (56,7%) of the CONSORT checklist the adherence score of the eligible RCTs was equal or greater than 75%. Seven items (18,9%) of the checklist were reported in all the examined trials (100%).

The absolute numbers and percentages of RCTs adherent per CONSORT item are presented in **Table 2**. A graphical presentation of adherence per CONSORT item is shown in **figure 2**.

**Table 2**: Absolute numbers and percentages of RCTs adherent per CONSORT item

| Section/Topic | Item No | Description | Number of RCTs (n=12) | CONSORT adherence (%) |
|---|---|---|---|---|
| **Title and abstract** | 1a | Identification as a randomized trial in the title | **5/12** | **41,7%** |
| | 1b | Structured summary of trial design, methods, results, and conclusions | **10/12** | **83,3%** |
| **Introduction** | 2a | Scientific background and explanation of rationale | **12/12** | **100%** |
| | 2b | Specific objectives or hypotheses | **12/12** | **100%** |
| **Methods** | | | | |
| Trial design | 3a | Description of trial design (such as parallel, factorial) including allocation ratio | **11/12** | **91,7%** |
| | 3b | Important changes to methods after trial commencement (such as eligibility criteria), with reasons | **2/12** | **16,7%** |
| Participants | 4a | Eligibility criteria for participants | **12/12** | **100%** |
| | 4b | Settings and locations where the data were collected | **11/12** | **91,7%** |
| Interventions | 5 | The interventions for each group with sufficient details to allow replication, including how and when they were actually administered | **7/12** | **58,3%** |
| Outcomes | 6a | Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed | **11/12** | **91,7%** |
| | 6b | Any changes to trial outcomes after the trial commenced, with reasons | **2/12** | **16,7%** |
| Sample size | 7a | How sample size was determined | **8/12** | **66,7%** |
| | 7b | When applicable, explanation of any interim analyses and stopping guidelines | **5/12** | **41,7%** |
| **Randomization** | | | | |
| Sequence generation | 8a | Method used to generate the random allocation sequence | **10/12** | **83,3%** |
| | 8b | Type of randomization; details of any restriction (such as blocking and block size) | **7/12** | **58,3%** |
| Allocation concealment | 9 | Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned | **7/12** | **58,3%** |
| Implementation | 10 | Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions | **4/12** | **33,3%** |
| Blinding | 11a | If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how | **5/12** | **41,7%** |
| | 11b | If relevant, description of the similarity of interventions | **2/12** | **16,7%** |
| Statistical methods | 12a | Statistical methods used to compare groups for primary | **12/12** | **100%** |

| | | | | |
|---|---|---|---|---|
| | | and secondary outcomes | | |
| | 12b | Methods for additional analyses, such as subgroup analyses and adjusted analyses | **6/12** | **50%** |
| **Results** | | | | |
| Participant flow | 13a | For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome | **11/12** | **91,7%** |
| | 13b | For each group, losses and exclusions after randomization, together with reasons | **10/12** | **83,3%** |
| Recruitment | 14a | Dates defining the periods of recruitment and follow-up | **10/12** | **83,3%** |
| | 14b | Why the trial ended or was stopped | **4/12** | **33,3%** |
| Baseline data | 15 | A table showing baseline demographic and clinical characteristics for each group | **12/12** | **100%** |
| Numbers analyzed | 16 | For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups | **11/12** | **91,7%** |
| Outcomes and estimation | 17a | For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval) | **12/12** | **100%** |
| | 17b | For binary outcomes, presentation of both absolute and relative effect sizes is recommended | **2/12** | **16,7%** |
| Ancillary analyses | 18 | Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory | **5/12** | **41,7%** |
| Harms | 19 | All important harms or unintended effects in each group | **10/12** | **83,3%** |
| **Discussion** | | | | |
| Limitations | 20 | Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses | **10/12** | **83,3%** |
| Generalizability | 21 | Generalisability (external validity, applicability) of the trial findings | **2/12** | **16,7%** |
| Interpretation | 22 | Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence | **12/12** | **100%** |
| **Other information** | | | | |
| Registration | 23 | Registration number and name of trial registry | **11/12** | **91,7%** |
| Protocol | 24 | Where the full trial protocol can be accessed, if available | **9/12** | **75%** |
| Funding | 25 | Sources of funding and other support (such as supply of drugs), role of funders | **10/12** | **83,3%** |

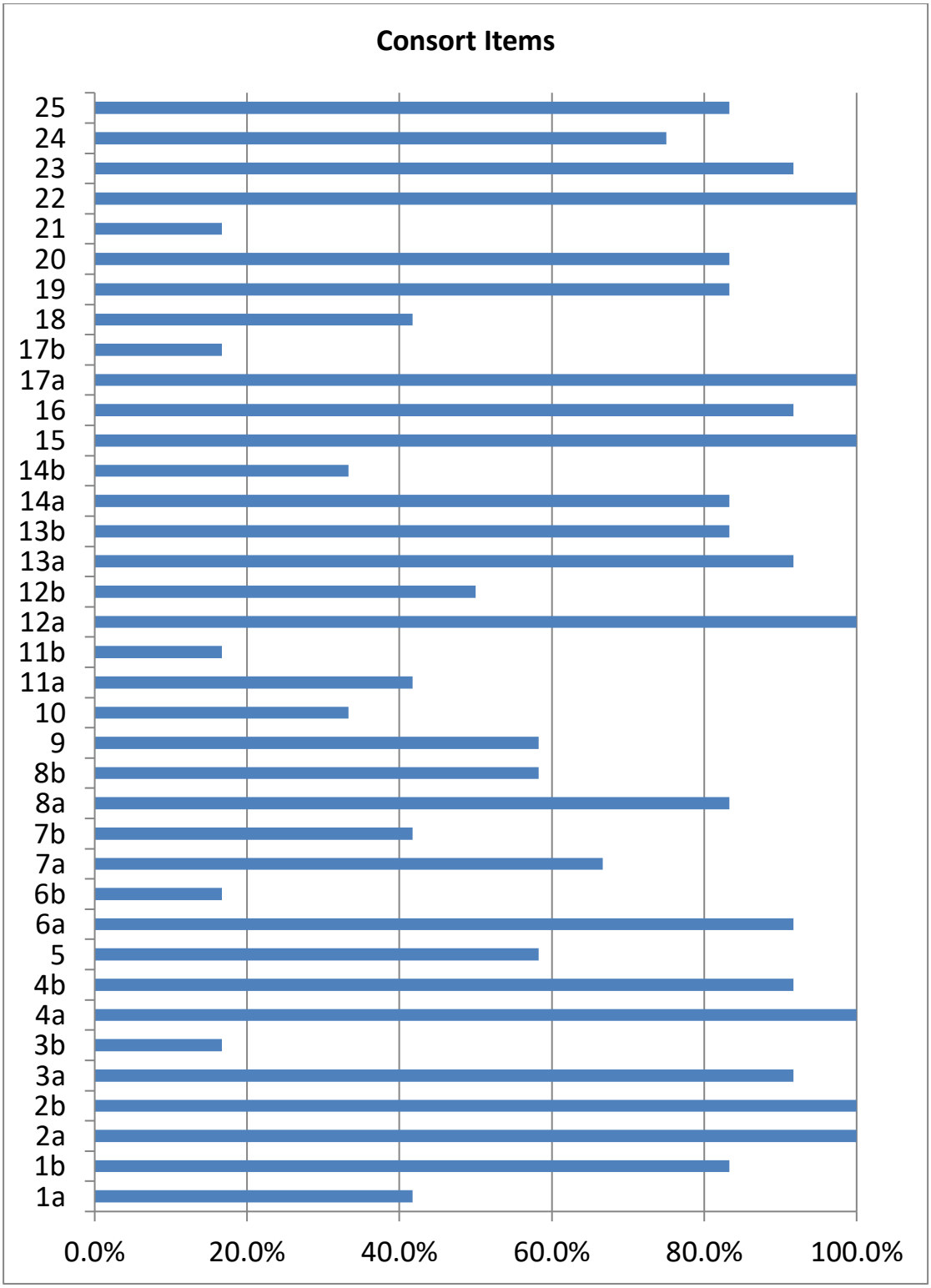


**Fig.2: Graphical presentation of adherence per CONSORT item**

## E. DISCUSSION

In this study, we used the CONSORT statement 2010 to evaluate the reporting quality of all the RCTs conducted and published during the Covid19 pandemic, examining the efficacy of the Interleukin-6 Receptor Antagonist, tocilizumab, in hospitalized patients with symptomatic coronavirus disease. This is a treatment that has been used off-label in Covid-19; however, randomized, controlled trials to date have largely been negative, with the most positive study showing a decreased risk of mechanical ventilation but no benefit on survival.

Twelve articles written in English fulfilled the criteria of randomized controlled studies. The CONSORT compliance score of the eligible trials ranged from 40,5% (minimum) to 86,5% (maximum), with a median value of 73%. Reporting quality was regarded as moderate, considering a cut-off value of 75% as adequate, in consistency with a number of published studies. Half of the RCTs had a compliance score ≥ 75% and were assessed as adequately reported. An association between IF and reporting quality has been previously suggested, but this finding was not confirmed by some authors. In our study, the mean CONSORT adherence score was significantly greater in the highest ranked journals, which are also CONSORT endorsing.

Allocation concealment (item 9), implementation (item 10) and blinding (items 11a and 11b) were among the least reported items. According to previous reports, only 18% of all randomised trials indexed on PubMed, reported any allocation concealment mechanism. Failure to adequately conceal the random allocation sequence until interventions are assigned may contribute to bias in estimating treatment effects. Those who enroll or obtain informed consent from participants should not be aware of the next assignment in the sequence, in order to avoid selection bias.

Blinding cannot always be implemented. Still, it is recommended that the authors should always state who was blinded, regardless of whether blinding is possible, (that is, participants, healthcare providers, data collectors, and those assessing outcomes). Notably, in the assessed trials, blinding was not applicable in 9 out of the 12 RCTs (75%), as they were open-label. Three trials (25%) were double-blind, placebo-controlled, but in only two of them there was an adequate reporting of the blinding procedure (in supplementary material). As stated by some authors, an open label design certainly poses a significant limitation, in estimating the treatment

effect. However, the possibility of conducting a robust double-blind placebo-controlled trial in a period of emergency is challenging. In addition, as it has been consistently reported and clinically observed, this monoclonal antibody rapidly lowers fever and serum CRP level in patients with COVID-19, thus making allocation concealment unlikely.

As most of the studies were multicenter, there was a lack of standardized treatment across trial sites and countries. Although 'standard' or 'usual' care provided according to local practices was not thoroughly described, item 5 (interventions) was positively appraised, unless drug intervention was not sufficiently reported.

Item 24 (where the full trial protocol can be accessed, if available) although the most underreported item in a previous relevant study (Rikos et al), in the current assessment it was reported in 9 RCTs (75%). Moreover, items involving interpretation of the results, trial limitations, sources of potential bias, registration number and funding issues are well-reported in more than 80% of the studies. In contrast, comments regarding generalizability to other populations (external validity and applicability of the trial findings) are reported in only 2 (16,7%) of the studies.

## F. CONCLUSION

In conclusion, a moderate adherence to the CONSORT statement was found in randomized controlled studies questioning the efficacy of tocilizumab in hospitalized Covid19 patients. Methodology reporting, especially sample size calculation, allocation concealment and implementation issues could be further improved.

## REFERENCES


- WHO Coronavirus Disease (COVID-19) Dashboard. World Health Organization, 2020. https://Covid19.who.int/.
- Moore JB, June CH. Cytokine release syndrome in severe COVID-19. Science 2020;368:473-4. doi:10.1126/science.abb8925
- 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. doi:10.1172/JCI137244
- http://www.consort-statement.org/

- Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, Elbourne D, Egger M, Altman DG. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomized trials. BMJ. 2010;340:c869.
- Ziogas DC, Zintzaras E. Analysis of the quality of reporting of randomized controlled trials in acute and chronic myeloid leukemia, and myelodysplastic syndromes as governed by the CONSORT statement. Ann Epidemiol. 2009 Jul; 19(7):494-500.
- Rikos D, Dardiotis E, Aloizou A-M, Siokas V, Zintzaras E, Hadjigeorgiou GM. Reporting Quality of Randomized Controlled Trials in Restless Legs Syndrome Based on the CONSORT Statement. Tremor and Other Hyperkinetic Movements. 2019;9. DOI: http://doi.org/10.5334/tohm.457
- https://clarivate.com/webofsciencegroup/solutions/journal-citation-reports/
- Hopewell S, Dutton S, Yu LM et al (2010) The quality of reports of randomised trials in 2000 and 2006: comparative study of articles indexed in PubMed. BMJ 340:723. https ://doi.org/10.1136/bmj.c723
- Plint AC, Moher D, Morrison A et al (2006) Does the CONSORT checklist improve the quality of reports of randomized controlled trials? A systematic review. Med J Aust 185:263–267
- Huwiler-Müntener K, Jüni P, Junker C et al (2002) Quality of reporting of randomized trials as a measure of methodologic quality. JAMA 287(21):2801–2804


**APPENDIX 1:** List of the RCTs included in the assessment study


1. Hermine O, Mariette X, Tharaux PL, Resche-Rigon M, Porcher R, Ravaud P; CORIMUNO-19 Collaborative Group. Effect of Tocilizumab vs Usual Care in Adults Hospitalized with COVID-19 and Moderate or Severe Pneumonia: A Randomized Clinical Trial. JAMA Intern Med. 2021 Jan 1;181(1):32-40. doi: 10.1001/jamainternmed.2020.6820. Erratum in: JAMA Intern Med. 2021 Jan 1;181(1):144. Erratum in: JAMA Intern Med. 2021 Jul 1;181(7):1021. PMID: 33080017; PMCID: PMC7577198.
2. Stone JH, Frigault MJ, Serling-Boyd NJ, Fernandes AD, Harvey L, Foulkes AS, Horick NK, Healy BC, Shah R, Bensaci AM, Woolley AE, Nikiforow S, Lin N,

Sagar M, Schrager H, Huckins DS, Axelrod M, Pincus MD, Fleisher J, Sacks CA, Dougan M, North CM, Halvorsen YD, Thurber TK, Dagher Z, Scherer A, Wallwork RS, Kim AY, Schoenfeld S, Sen P, Neilan TG, Perugino CA, Unizony SH, Collier DS, Matza MA, Yinh JM, Bowman KA, Meyerowitz E, Zafar A, Drobni ZD, Bolster MB, Kohler M, D'Silva KM, Dau J, Lockwood MM, Cubbison C, Weber BN, Mansour MK; BACC Bay Tocilizumab Trial Investigators. Efficacy of Tocilizumab in Patients Hospitalized with Covid-19. N Engl J Med. 2020 Dec 10;383(24):2333-2344. doi: 10.1056/NEJMoa2028836. Epub 2020 Oct 21. PMID: 33085857; PMCID: PMC7646626.

3. Salama C, Han J, Yau L, Reiss WG, Kramer B, Neidhart JD, Criner GJ, Kaplan-Lewis E, Baden R, Pandit L, Cameron ML, Garcia-Diaz J, Chávez V, Mekebeb-Reuter M, Lima de Menezes F, Shah R, González-Lara MF, Assman B, Freedman J, Mohan SV. Tocilizumab in Patients Hospitalized with Covid-19 Pneumonia. N Engl J Med. 2021 Jan 7;384(1):20-30. doi: 10.1056/NEJMoa2030340. Epub 2020 Dec 17. PMID: 33332779; PMCID: PMC7781101.
4. Salvarani C, Dolci G, Massari M, Merlo DF, Cavuto S, Savoldi L, Bruzzi P, Boni F, Braglia L, Turrà C, Ballerini PF, Sciascia R, Zammarchi L, Para O, Scotton PG, Inojosa WO, Ravagnani V, Salerno ND, Sainaghi PP, Brignone A, Codeluppi M, Teopompi E, Milesi M, Bertomoro P, Claudio N, Salio M, Falcone M, Cenderello G, Donghi L, Del Bono V, Colombelli PL, Angheben A, Passaro A, Secondo G, Pascale R, Piazza I, Facciolongo N, Costantini M; RCT-TCZ-COVID-19 Study Group. Effect of Tocilizumab vs Standard Care on Clinical Worsening in Patients Hospitalized With COVID-19 Pneumonia: A Randomized Clinical Trial. JAMA Intern Med. 2021 Jan 1;181(1):24-31. doi: 10.1001/jamainternmed.2020.6615. PMID: 33080005; PMCID: PMC7577199.
5. Zhao H, Zhu Q, Zhang C, Li J, Wei M, Qin Y, Chen G, Wang K, Yu J, Wu Z, Chen X, Wang G. Tocilizumab combined with favipiravir in the treatment of COVID-19: A multicenter trial in a small sample size. Biomed Pharmacother. 2021 Jan;133:110825. doi: 10.1016/j.biopha.2020.110825. Epub 2020 Sep 30. PMID: 33378989; PMCID: PMC7524677.
6. Veiga VC, Prats JAGG, Farias DLC, Rosa RG, Dourado LK, Zampieri FG, Machado FR, Lopes RD, Berwanger O, Azevedo LCP, Avezum Á, Lisboa TC, Rojas SSO, Coelho JC, Leite RT, Carvalho JC, Andrade LEC, Sandes AF, Pintão MCT, Castro CG Jr, Santos SV, de Almeida TML, Costa AN, Gebara OCE, de

Freitas FGR, Pacheco ES, Machado DJB, Martin J, Conceição FG, Siqueira SRR, Damiani LP, Ishihara LM, Schneider D, de Souza D, Cavalcanti AB, Scheinberg P; Coalition covid-19 Brazil VI Investigators. Effect of tocilizumab on clinical outcomes at 15 days in patients with severe or critical coronavirus disease 2019: randomised controlled trial. BMJ. 2021 Jan 20;372:n84. doi: 10.1136/bmj.n84. PMID: 33472855; PMCID: PMC7815251.

7. Rosas IO, Bräu N, Waters M, Go RC, Hunter BD, Bhagani S, Skiest D, Aziz MS, Cooper N, Douglas IS, Savic S, Youngstein T, Del Sorbo L, Cubillo Gracian A, De La Zerda DJ, Ustianowski A, Bao M, Dimonaco S, Graham E, Matharu B, Spotswood H, Tsai L, Malhotra A. Tocilizumab in Hospitalized Patients with Severe Covid-19 Pneumonia. N Engl J Med. 2021 Apr 22;384(16):1503-1516. doi: 10.1056/NEJMoa2028700. Epub 2021 Feb 25. PMID: 33631066; PMCID: PMC7953459.
8. Wang D, Fu B, Peng Z, Yang D, Han M, Li M, Yang Y, Yang T, Sun L, Li W, Shi W, Yao X, Ma Y, Xu F, Wang X, Chen J, Xia D, Sun Y, Dong L, Wang J, Zhu X, Zhang M, Zhou Y, Pan A, Hu X, Mei X, Wei H, Xu X. Tocilizumab in patients with moderate or severe COVID-19: a randomized, controlled, open-label, multicenter trial. Front Med. 2021 Jun;15(3):486-494. doi: 10.1007/s11684-020-0824-3. Epub 2021 Mar 9. PMID: 33687643; PMCID: PMC7940448.
9. Hamed DM, Belhoul KM, Al Maazmi NA, Ghayoor F, Moin M, Al Suwaidi M, Narainen M, Makki M, AbdulRahman M. Intravenous methylprednisolone with or without tocilizumab in patients with severe COVID-19 pneumonia requiring oxygen support: A prospective comparison. J Infect Public Health. 2021 Aug;14(8):985-989. doi: 10.1016/j.jiph.2021.06.003. Epub 2021 Jun 10. PMID: 34153729; PMCID: PMC8191304.
10. REMAP-CAP Investigators, Gordon AC, Mouncey PR, Al-Beidh F, Rowan KM, Nichol AD, Arabi YM, Annane D, Beane A, van Bentum-Puijk W, Berry LR, Bhimani Z, Bonten MJM, Bradbury CA, Brunkhorst FM, Buzgau A, Cheng AC, Detry MA, Duffy EJ, Estcourt LJ, Fitzgerald M, Goossens H, Haniffa R, Higgins AM, Hills TE, Horvat CM, Lamontagne F, Lawler PR, Leavis HL, Linstrum KM, Litton E, Lorenzi E, Marshall JC, Mayr FB, McAuley DF, McGlothlin A, McGuinness SP, McVerry BJ, Montgomery SK, Morpeth SC, Murthy S, Orr K, Parke RL, Parker JC, Patanwala AE, Pettilä V, Rademaker E, Santos MS, Saunders CT, Seymour CW, Shankar-Hari M, Sligl WI, Turgeon AF, Turner AM, van de

Veerdonk FL, Zarychanski R, Green C, Lewis RJ, Angus DC, McArthur CJ, Berry S, Webb SA, Derde LPG. Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19. N Engl J Med. 2021 Apr 22;384(16):1491-1502. doi: 10.1056/NEJMoa2100433. Epub 2021 Feb 25. PMID: 33631065; PMCID: PMC7953461.

11. Soin AS, Kumar K, Choudhary NS, Sharma P, Mehta Y, Kataria S, Govil D, Deswal V, Chaudhry D, Singh PK, Gupta A, Agarwal V, Kumar S, Sangle SA, Chawla R, Narreddy S, Pandit R, Mishra V, Goel M, Ramanan AV. Tocilizumab plus standard care versus standard care in patients in India with moderate to severe COVID-19-associated cytokine release syndrome (COVINTOC): an open-label, multicentre, randomised, controlled, phase 3 trial. Lancet Respir Med. 2021 May;9(5):511-521. doi: 10.1016/S2213-2600(21)00081-3. Epub 2021 Mar 4. PMID: 33676589; PMCID: PMC8078880.

12. Rashad A, Mousa S, Nafady-Hego H, Nafady A, Elgendy H. Short term survival of critically ill COVID-19 Egyptian patients on assisted ventilation treated by either Dexamethasone or Tocilizumab. Sci Rep. 2021 Apr 23;11(1):8816. doi: 10.1038/s41598-021-88086-x. PMID: 33893337; PMCID: PMC8065149.