

# Combination therapy of Tocilizumab and steroid for COVID-19 patients: A meta-analysis

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## Systematic Review

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# Abstract

## Background

The coagulation markers, pro-inflammatory cytokines (such as IL-2R, IL-6, IL-10, and TNF-a) and Lymphopenia are associated with the severity of COVID-19 disease. The use of anti-inflammatory agents such as corticosteroids (CS) or Tocilizumab (TCZ) has been suggested for the treatment of advanced stage of COVID-19 and reduction of mechanical ventilators and mortality. The aim of this meta-analysis is to determine the role of combination therapy with Tocilizumab and steroid in COVID-19 patient.

## Material and methods

Relevant studies were found using online international databases and suitable studies were selected and assessed by two independent researchers. The quality of all papers were determined by a checklist. Heterogeneity assay among the primary studies was evaluated by Cochran's Q test and I2 index. The statistical analyses were done using Stata ver. 14 package (StataCorp, College Station, TX, USA) software. Publication bias was estimated through the Egger's test and the impact of each study on the overall estimate was assessed by sensitivity analysis.

## Result

6 studies were entered into this meta-analysis. The results of these studies showed that the risk of death for COVID-19 patients treated with the combination of corticosteroids and Tocilizumab compared to Tocilizumab or [C1] control group was 0.74 (95% CI: 0.36-1.50) and 0.48(95% CI: 0.31-0.74) respectively.

## Conclusion

This meta-analysis showed that the risk of death in COVID-19 patients who treated with Corticosteroids and Tocilizumab was lower than Tocilizumab and control group (26% and 52% respectively).

## Introduction

The novel coronavirus (2019-nCoV, or COVID-19) was reported in China's Wuhan city, in December 2019 and spread rapidly as a global health problem. Several syndromes with clinical manifestations are associated with this infection such as pneumonia, respiratory failure and death **(1)**.

Generally, most patients have reported mild illness, and approximately 10% of them require intensive care unit (ICU) due to pneumonia and acute respiratory distress syndrome (ARDS). It is reported that, the clinical course of COVID-19 is characterized by three different stages. In the early stage, a viral replication can cause flu-like symptoms. The second stage is usually accompanied by high fever and symptoms of pneumonia and decreasing of viremia. Most patients show the third and super-inflammatory phase**(2, 3)**. In this stage it is observed the levels of inflammatory markers and coagulation (including reactive protein C) (CRP), ferritin, and D-dimer), pro-inflammatory cytokines (such as IL-2R, IL-6, IL-10, and TNF-a) and

lymphopenia. These factors are associated with the severity of COVID-19 disease (4, 5). In addition, Adult Respiratory Distress Syndrome (ARDS) is considered as an acute syndrome of lung inflammation and is the most common cause of death in this group of patients (6).

Due to the inflammatory status on COVID-19, steroids have been used as immunomodulatory agents. Recently, several studies have been done on the clinical benefits of steroids and corticosteroids and interferon inhibitors in COVID-19 patients(7) . In addition regarding viral infection, there are some guidelines have been suggested for the use of glucocorticoids and other immune-regulating agents (8). It is suggested that patients undergoing corticosteroid therapy as well as patients treated with interleukin appear to be better inhibitors than antiviral drugs and antibiotics. In addition, treatment based on combination of anti-inflammatory (corticoid therapy) and anticoagulant lead to less ventilation, hospitalization and finally lower morbidity and mortality (9). It is suggested that the use of anti-inflammatory agents such as corticosteroids (CS) or Tosituzumab (TCZ) might be useful for the treatment of advanced stage of COVID-19 and reduction of the mechanical ventilators and risk of mortality .(10) Mechanism of steroid is shown in fig.1.

According to the results of some studies, treatment of COVID-19 patients with CS alone or TCZ might lead to increased survival. It seems that combination therapy of TCZ /CS can be used to modulating inflammation of lung injury (11). Therefore, the aim of this meta-analysis study is to determine the role of combination therapy with TCZ /CS in COVID-19 patients.

## Materials And Methods

### Search strategy

In this study, the published articles were collected from databases such as Science direct, Pub med, Web of Science, Scopus, Cochrane and Google scholar between January 2019 to April 2021. The search strategy was performed using English keywords as well as combination of important, and sensitive words. Search was done using the keywords "Tosituzumab", "Clinical trial", "COVID-19", "RR", "SARS-COV-2", "Risk Ratio", "Steroids", "Corticosteroids", "Methylprednisolone" by adding AND, OR in the title and abstract. In addition, the reference of articles was examined for the increasing of the search sensitivity. Finally, all references entered into reference management software (EndNote).

### Inclusion criteria

In this research, the search strategy tool (PICO) aimed to determine the impact of patient (P), intervention (I), comparison (C), and outcome (O). "P" signifies COVID-19 patients in studies; "I" means intervention with Tosituzumab and steroids. "C" includes three groups of patients: 1- COVID-19 patients who treated with Tosituzumab and steroids. 2- COVID-19 patients who did receive Tosituzumab alone 2: COVID-19 patients who did receive standard of care treatment (control). "O" means the effectiveness of the Tosituzumab and steroids in case group.

All clinical trial studies were included in this meta-analysis for evaluating the efficacy of Tosituzumab and steroids in treatment of COVID-19.

### **Exclusion criteria**

1- Those studies that scored less than 5 based on the quality assessment checklist. 2- Studies those patients treated with other antivirals 5. Case reports or case series studies. 5- Studies in non-English language.

### **Selection studies**

In this study, the full text or summary of articles, documents and reports were screened and extracted. Firstly, the irrelevant articles were removed from this study. Then, by reviewing and studying, the case reports and review studies were omitted. Finally, according to inclusion and exclusion criteria, data were extracted from full-text articles.

### **Extracting the data**

Screening and data extraction were performed by two independent reviewers based on article title, first author's name, year of study, journal name, place of study, type of study, total number of patients in TCZ +/- CS group, number of recovered patients in TCZ +/- CS group, number of deaths in TCZ +/- CS group, total number of patients in control group, number of recovered patients in control group, and number of deaths in control group were entered into the excel.

### **Evaluation of quality**

In this study, Newcastle-Ottawa scale (NOS) checklist (12) was used for the evaluation of the quality of articles. In this checklist, 9 questions were presented that cover the type of study, sample size, study objectives, study population, sampling method, data analysis method, presentation of findings in an appropriate way and presentation of results based on objectives. Each question was assigned a score. If a study scored at least 5 points, it was included in this study.

### **Analysis**

Stata ver. 14 package (Stata Corp, College Station, TX, USA) was used to analyze the obtained data. Data were weighted and combined based on the inverse variance. Cochran (Q) and  $I^2$  tests were used to determine heterogeneity index between studies. Based on the heterogeneity results, a random effect model was used to estimate the risk of death in different types of treatment groups. Publication bias was estimated through the Egger's test and the impact of each study on the overall estimate was assessed by sensitivity analysis.

## **Results**

Table 1: primary studies included in a meta-analysis (Corticosteroids and Tocilizumab v.s Tocilizumab).

First Author, Publication Year	Area of Study	Type of Study	Case Number of patients (TCZ +/CS [C1])	Case Number of deaths in group (TCZ +/ CS)	Control Number of patients (TCZ )	Control Number of deaths in group (TCZ )	Reference
Van den Eynde (2021)	Spain	Cohort	78	23	21	7	(11)
Rodríguez-Bano (2021)	Spain	Cohort	151	19	88	2	(13)
Ruiz-Antora'n (2021)	Spain	Cohort	119	13	149	32	(14)
Mikulska (2020)	Italy	Cohort	56	5	29	4	(15)
Sanz Herrero (2021)	Spain	observational	56	11	16	10	(16)
Total			460	71	303	55	

Table 1: primary studies included in a meta-analysis (Corticosteroids and Tocilizumab v.s Tocilizumab) [C1]

Table 2: Sensitivity analysis for evaluation of the effect of initial studies on the overall performance estimation of Corticosteroids and Tocilizumab v.s Tocilizumab group

Study omitted	Estimate	[95% Conf. Interval]
Van den Eynde (Spain)	.72801846	.29042196-1.8249683
Rodríguez-Bano (Spain)	.52766854	.33329785-.83539116
Ruiz-Antoran (Spain)	.87784004	.32174429-2.3950796
Mikulska (Italy)	.77413857	.33369735-1.7959104
Sanz Herrero (Spain)	.95582867	.4291811-2.1287246
Combined	.73691619	.36249574-1.4980741

Table 3: primary studies included in a meta-analysis (Corticosteroids and Tocilizumab v.s control).

Year	Area of Study	Type of Study	Case Number of patients (TCZ +/-CS )	Case Number of deaths in group (TCZ +/- CS)	Number of patients in control group	Number of deaths in control group	Reference
	Spain	Cohort	78	23	118	69	(11)
2020	Spain	Cohort	151	19	344	41	(13)
2020	Spain	Cohort	119	13	151	40	(14)
	Italy	Cohort	56	5	66	23	(15)
	Spain	Cohort	163	13	211	51	(9)
			567	73	890	224	

Table 4: Sensitivity analysis for evaluation of the effect of initial studies on the overall performance estimation of Corticosteroids and Tocilizumab v.s control group.

Study omitted	Estimate	[95% Conf.Interval]
Van den Eynde (Spain)	.4577536	.24162339-.86721057
Rodriguez-Bano (Spain)	.41704786	.32034466-.54294306
Ruiz-Antoran (Spain)	.48821339	.27956277-.85258967
Mikulska (Italy)	.52491945	.3288298-.83794242
Luis (Spain)	.5208813	.31243503-.86839598
Combined	.47637601	.30570779-.74232358

## Discussion

The aim of this meta-analysis study was to evaluate the efficacy of Corticosteroids and Tocilizumab on the risk of death in COVID-19 patients. The results showed that the risk of mortality in patients who treated with Corticosteroids and Tocilizumab was lower than (26%) in patients treated with Tocilizumab alone. There was no statistically significant difference. By omitting the Rodriguez-Bano study the risk of death in patients treated with Corticosteroids and Tocilizumab was significantly lower than (47%) in patients treated with Tocilizumab alone. In addition, the risk of mortality in patients who treated with Corticosteroids and Tocilizumab was significantly lower than (52%) the control group (the group that received routine treatment).

At the beginning of the epidemic, corticosteroid therapy was one of the most controversial drug against COVID-19 (9). In general, steroids, including corticosteroids and glucocorticoids (dexamethasone and methylprednisolone), are used as immunosuppressive therapies in COVID-19 patients who suffer from severe inflammation by high levels of pro-inflammatory cytokines IL-6 and IL-1 and play an important role in reducing mortality, mechanical ventilation as well as increasing survival in covid-19 patients (17) (18).

Tocilizumab, a monoclonal antibody against IL-6, is one of the drugs recommended at the beginning of the pandemic in China and Italy, in patients revealed severe inflammation and elevated ferritin and IL-6 levels ( $\text{PaO}_2 / \text{FiO}_2 < 150$ ) (19). Observational studies in Spain, Italy, and the United States show that TCZ reduces ICU and mechanical ventilation as well as mortality in patients compared to the SOC group (10). In addition, another study in Italy suggested that the rate of mortality in TCZ group (179 patients) was significantly lower than control group (365 patients) (20).

Another finding reported that the use of corticosteroids, or TCZ, has been widely used in COVID-19 patients with severe pneumonia. Some, studies show that treatment with the combination of corticosteroids and tocilizumab reduce in-hospital mortality. Also there was no intubation observed during 48 hours (11) (21). In addition, in a study conducted in Italy, the use of these two drugs was investigated either separately or in combination to treat COVID-19 patients. It is found that administration of TCZ and corticosteroids are need for evaluating the effectiveness and safety (22). A cohort study by Narain et al., shown that combination of corticosteroids and TCZ for the treatment of patients increased survival compared to the SOC group or the group receiving corticosteroids alone (23). Other observational study showed that combination treatment with steroids and TCZ had better results than steroids added at a later stage.

The results of the present studies indicate that combination of corticosteroids and tocilizumab is safe and effective in the treatment of covid-19 patients. The effect of this anti-inflammatory compound requires further RCT studies.

## Conclusion

This meta-analysis showed that the risk of death in COVID-19 patients who treated with Corticosteroids and Tocilizumab was lower than Tocilizumab and control group (26% and 52% respectively).

## Declarations

Competing interests: The authors declare no competing interests.

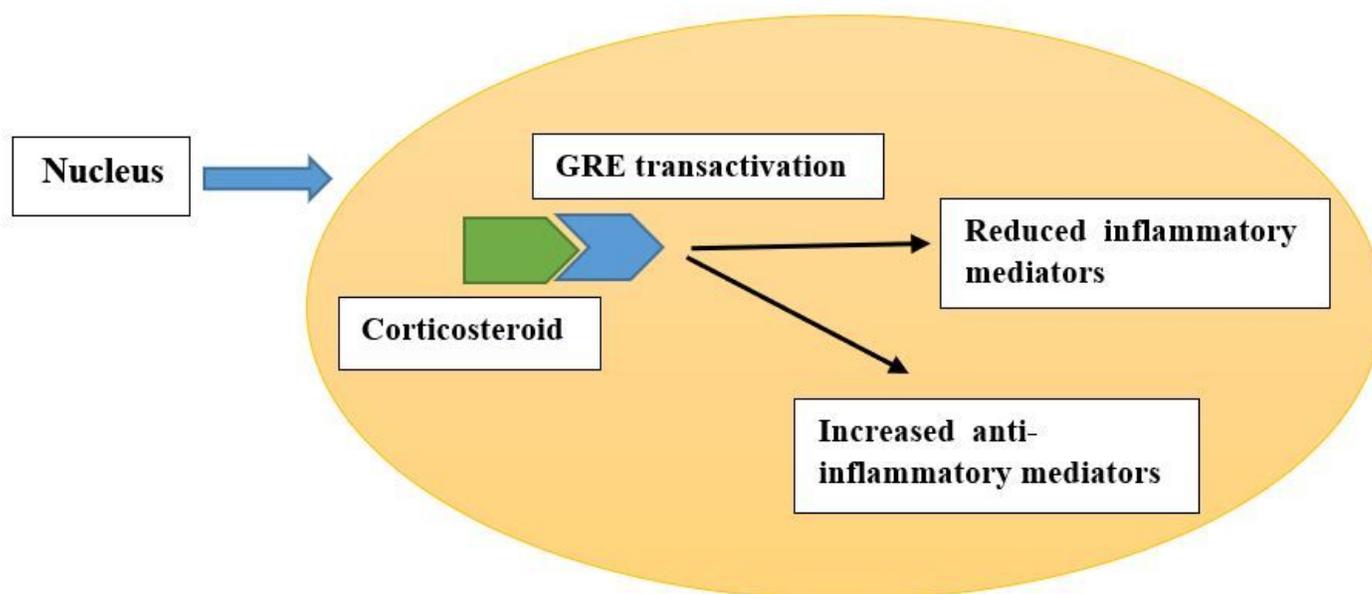
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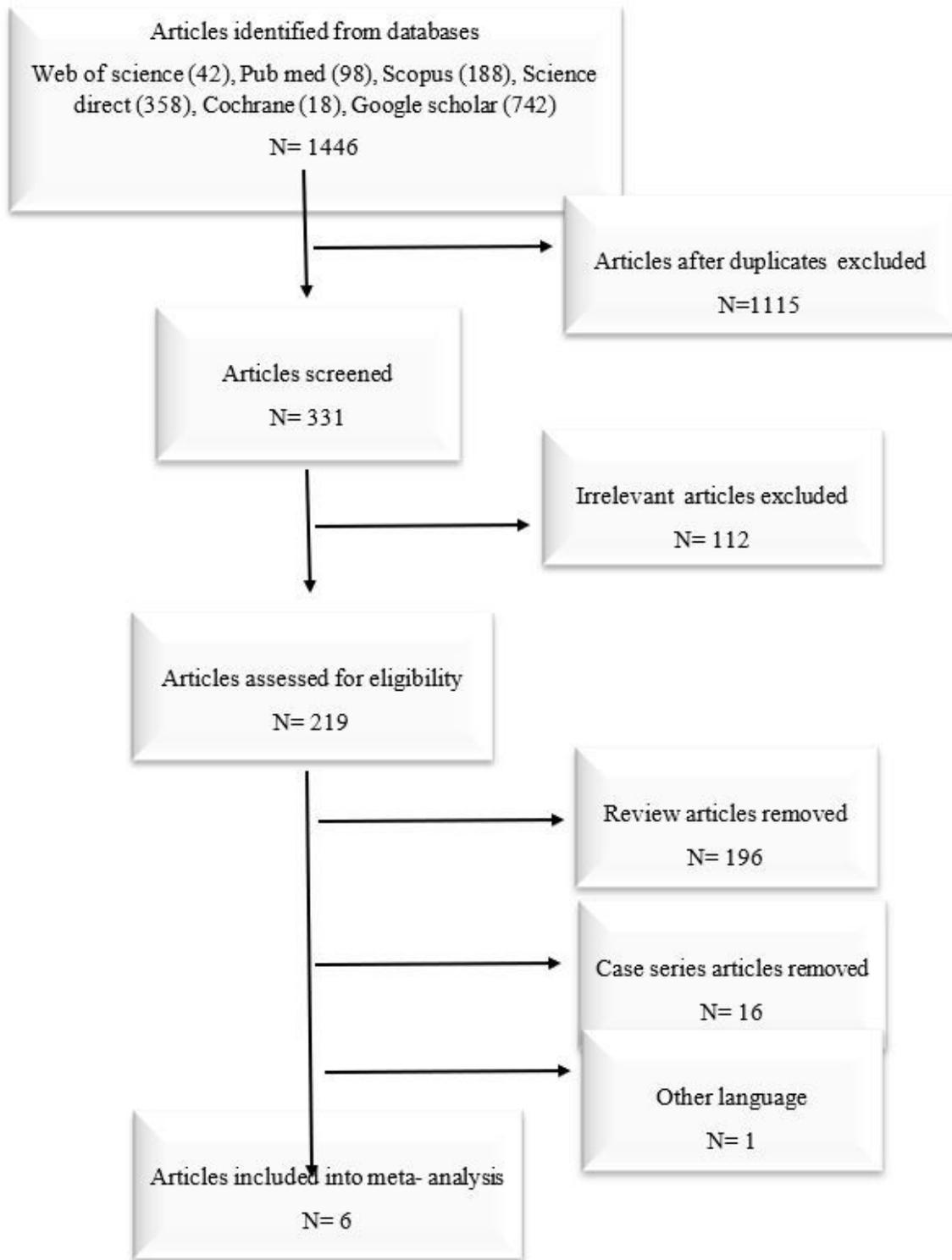
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## Figures



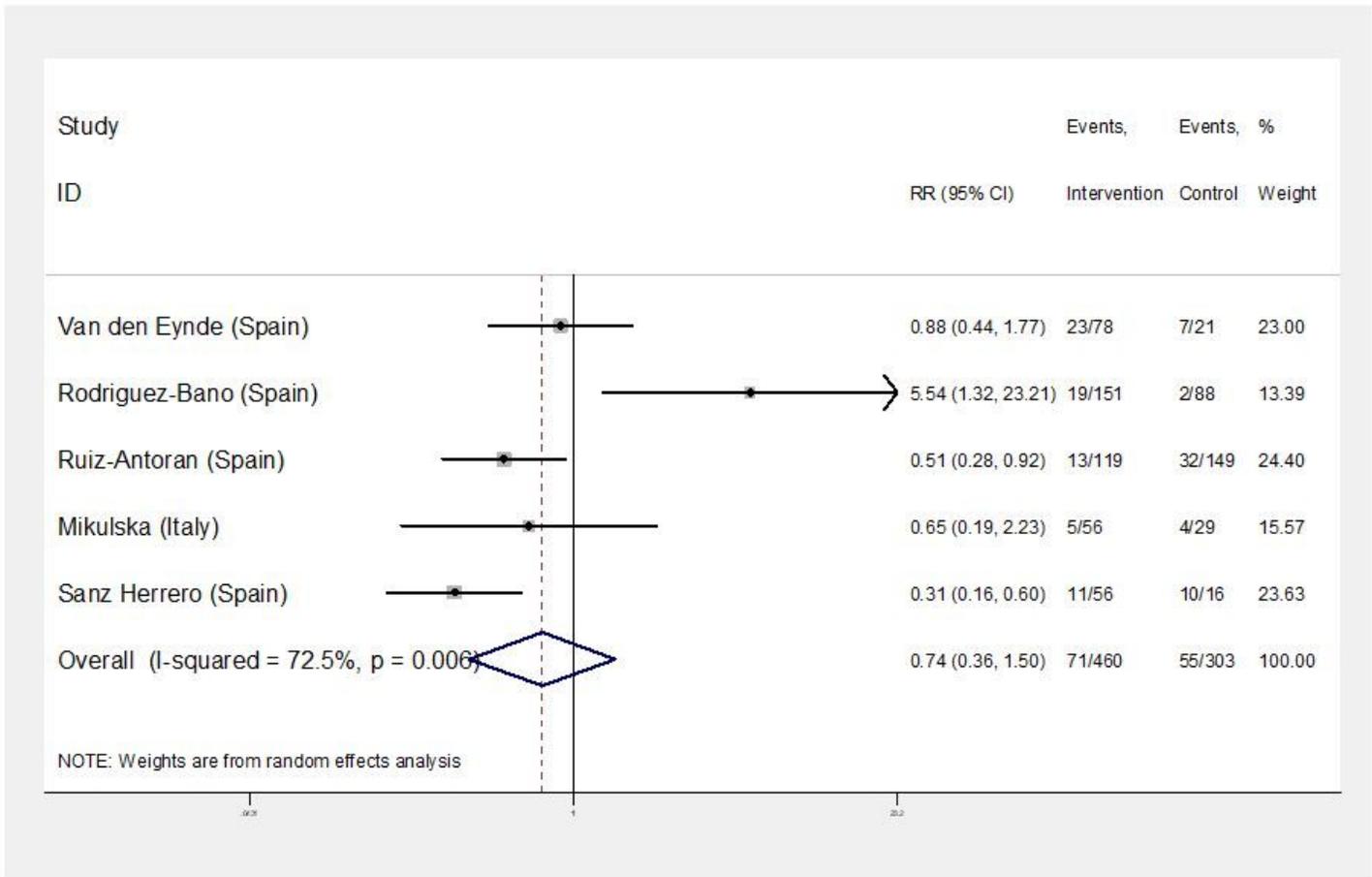
**Figure 1**

mechanism of Corticosteroid



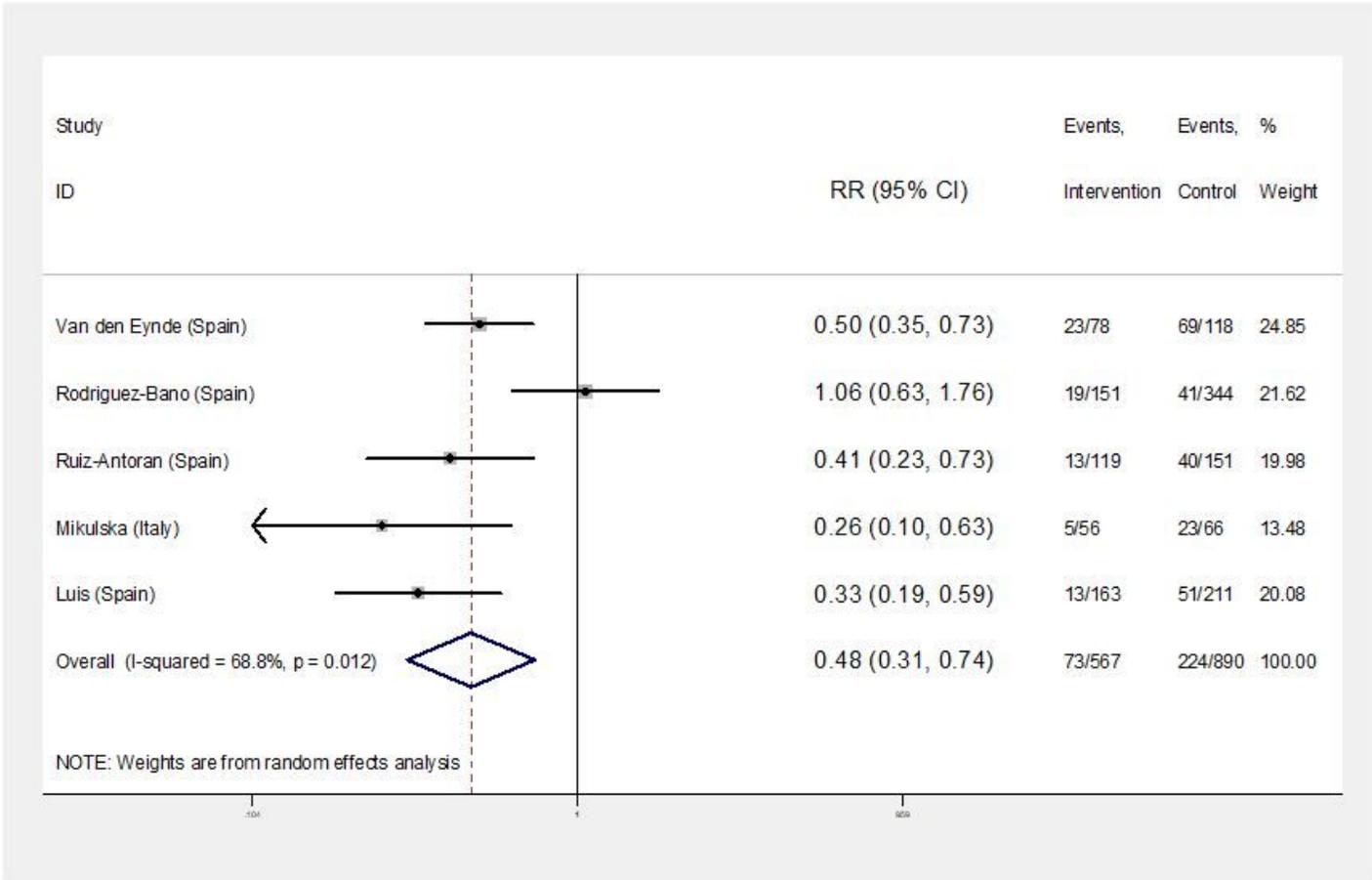
**Figure 2**

flowchart of primary studies included in to meta-analysis



**Figure 3**

Forest plot of the risk of death in COVID-19 patients treated with Corticosteroids and Tocilizumab v.s Tocilizumab in initial studies and the overall estimate



**Figure 4**

Forest plot of the risk of death in COVID-19 patients treated with Corticosteroids and Tocilizumab v.s control (Routine treatment) in initial studies and the overall estimate