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The Effect of Tocilizumab in the Treatment of COVID-19 Patients: A Propensity Score-Matched and a Stabilized Inverted Probability of Treatment Weight Study (SIPTW)

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Abstract: Studies disputed the use of tocilizumab in the treatment of COVID-19 patients, retrospective studies and one interventional study from the RECOVER study supported tocilizumab use, however, many other interventional and a retrospective propensity score-matched studies did not find a benefit from its use, in contrast, increased mortality was demonstrated, this study aims to add knowledge on this topic. Records for 1124 COVID-19 admitted patients were reviewed. Patients were recruited from three participating hospitals. Characteristics of all-cohort and propensity score-adjusted (PS-adjusted) patients were described, data was analyzed as propensity score matching (PSM) and a stabilized inverted probability of treatment weighting (SIPTW). Management of patients was up to the treating physicians who varied in the treatment approach., the effect difference was estimated by $\chi 2$. Further, the study was analyzed as logistic regression to assure robustness of the inferred outcomes; recovery, need for home oxygen, and all-cause mortality. All-cause mortality for patients was 12.7% (143) and in ICU was 54.0% (128). In the all-cohort, there was an increase of patients' recovery in controls; 39.6% versus tocilizumab 9.9% (P<0.000). The need for home oxygen was more in tocilizumab; 59.2%, controls 38.6% (P<0.000). Mortality was higher in tocilizumab than the controls (25.4% versus 10.9%, P<0.000). Analyses as PSM-adjustment and SIPTW continued to demonstrate significantly less recovery and more mortality with using tocilizumab ($P \leq 0.002$), but tocilizumab and the control did not differ significantly for the need for home oxygen therapy (49.1% vs. 48.6% respectively, P=0.945). No benefit was seen for tocilizumab in the treatment of COVID-19 patients, quite the opposite, it showed no recovery benefit, increased mortality, and did not impact the need for home oxygen.

Keywords: Tocilizumab, COVID-19 Recovery, COVID-19 and Home Oxygen, COVID-19 Mortality

1. Introduction

The world devastation started from Wuhan, China, in December 2019 with the worldwide spread of the novel virus SARS-CoV-2, with over 209 million confirmed cases and over 4.4 million confirmed deaths [1, 2]. The fast spread of the virus superseded the previous coronavirus SARS-CoV in 2003, the pandemic influenza 2009 (H1N1pdm009), and the MERS-CoV [3-5].

In Jordan, the COVID-19 devastation started a few months after the diagnosis of an initial case in early March 2020, by 18 July 2021 there were over 788,000 infections recorded with over 10,000 dead patients [6]. Attempts at a curative therapy were pursued to save patients, many agents were investigated like antivirals [7-10], and convalescent plasma that did not demonstrate a clear therapeutic benefit in mortality, length of hospital stay, or mechanical ventilation [11, 12]. Interleukin-6 inhibitors were repeatedly evaluated for the treatment of COVID-19 patients, a solid conclusion is not yet reached. In the current study, we evaluate the interleukin-6 inhibitor (tocilizumab) therapeutic benefit in the treatment of COVID-19 patients employing PSM adjustment and SIPTW methods analyses in an attempt to obtain a robust conclusion.

2. Materials and Methods

2.1. Study Settings

Data for COVID-19 patients was collected from three participating hospitals (The Specialty, Jordan, and Al Khalidi) with a total bed capacity of around 700, special units for the management of patients with COVID-19 were allocated with an approximate capacity of 155-floor beds and 47 ICU beds. The study was a retrospective cross-sectional over 22 weeks (28 November 2020 to 6 May 2021, data was uploaded into a cloud excel sheet (*Microsoft Corporation*). Records were included as patients presented for admissions in the participating hospitals. The study was approved by each of the internal review boards of the three hospitals, no consent was needed.

2.2. Treatment Protocols

There is a current updated COVID-19 management protocol published by the Jordan Ministry of Health (MOH). In the three hospitals, the treating physicians partially relied on the MOH protocol and literature updates, which may have caused a heterogeneous management approach (supplementary material), agents administered differed; steroids (dexamethasone or solumedrol), anticoagulants (Enoxaparin sodium, Apixaban, Rivaroxaban, and Fondaparinux), Vitamin D tablets (used as a three-days 50,000 I.U. regimen before March 15, then a seven-days 50,000 I.U., also a 2000 I.U. and 5000 I.U. daily were prescribed), antivirals (Favipiravir, Remdesivir), acetyl-salicylic acid (ASA), colchicine, Zn tablets and Vitamin C (supplementary material), despite heterogeneity, the IL-6 inhibitor used as tocilizumab.

2.3. Classification of Radiological Findings

Chest radiography scoring system: the degree of lungs involvement was based on radiologists' reports to classify the degree of lungs involvement. Normal chest x-ray and/or normal CT chest with no infiltrate were considered as no involvement (score 1), a lobar infiltrate with 25% involvement (score 2), scattered ground glass appearance involving lungs with>25 - 50% involvement (score 3), diffuse patchy infiltrate>50 - 75% involvement was considered as (score 4), and multilobe infiltrate was considered as>75% involvement (score 5). The classification we used did not fit well with a previous one [13].

2.4. Statistical Analysis

Characteristics for the all-cohort and PS-adjusted patients were described. To propensity-score characteristics, match tolerance (caliper) was set at 0.1, without replacement, predictors were tested for the normal distribution by skewness, histogram, and Q-Q blot, all closely fitted a normal curves distribution, skewness for all were<1.0 and>-1.0, multicollinearity was evaluated by linear regression, tolerance was above 0.251, mostly>0.8 and VIF was mostly less than 1.3 except two with 3.554 and 3.992. Predicted probability was derived from continuous and binary predictors by logistic binary regression analysis, some continuous predictors were Log10 transformed to normalize the distribution before they were incorporated in the predicted probability model (supplementary material). Predictors entered were: Age, gender, comorbidities, body mass index, LDH level, ferritin level, interleukin 6 level, imaging categories, steroids, oxygen saturation, colchicine, antivirals, and documented temperature. Treatment (tocilizumab) and comparators were analyzed by Chi-square test (χ^2) for the difference in proportions, with post hoc analysis by Bonferroni adjusted p-value to assure balanced variables. SIPTW patients were estimated for the outcome effects [15], Logistic regression analysis was tabulated for the all-cohort, PSM and, SIPTW patients. SPSS version 25 with Python Essentials and Fuzzy extension command blog-ins was used in the analysis, significance was considered for values<0.05.

3. Results

The characteristics of the 1220 patients were reviewed, ninety-six cases were excluded due to missing data precluding analysis. Analysis was for 1124 as the all-cohort, and 228 PSM and 228 SIPTW analyzed patients (Table 1). The differences in characteristics between the tocilizumab treatment and controls among the all-cohort were balanced

with the PS index (Table 1), few characteristics had significant (P<0.05) but borderline imbalance with PSM adjustment. Age was balanced in the initial cohort except for the age group (66 – 75) years where more patients were in the controls, for the PSM patients all categories were balanced. Gender remained well-balanced in the initial cohort (P=0.330) and the PSM-adjusted patients (P=0.778). Antivirals favipiravir was proportionally (85.1%) prescribed more in the all-cohort (P<0.05), but remdesivir was significantly more (10.2%) in the PSM-adjusted patients who were on tocilizumab (P=0.015). Colchicine, antibiotics, and antifungals were imbalanced in the all-cohort patients but were balanced (P=NS) in the PSM-adjusted patients. There were significantly more patients with more symptoms in the tocilizumab patients (P<0.05), but diarrhea and rhinorrhea were balanced (P<NS), all symptoms and the documented fever were balanced on PSM-adjustment (P=NS). Comorbidities were balanced in the all-cohort and PSM-adjusted patients (P=NS), except for the "two or more" category it remained marginally imbalanced (P<0.05), where patients were proportionally more in the tocilizumab. BMI categories [14], and tobacco were balanced for both all-cohort and PSM-adjusted patients (P=NS). The admission blood oxygen saturation was imbalanced for the patients with saturations (<79, 86 – 90, and>90) but all were balanced in the PSM-patients (P=NS). Oxygen delivery methods for patients were imbalanced for the all-cohort patients (P<0.05), but all were balanced by PSM (P=NS) except for the nasal prongs and the nonrebreather mask remained significantly imbalanced (P<0.05). Admission radiological imaging (CT scan) showed less patients allocated to score 4 (>50 - 75% involvement, (P<0.05), and more patients allocated to tocilizumab in score 5 (>75% involvement, P<0.05), no PS-adjustment balance for 2, 4, 5 where more patients remained significantly more in tocilizumab (P<0.05)). High PCT levels, D-Dimer levels, C-RP and all serum ferritin levels [15] were imbalanced in the all-cohort patients, and were PSM balanced (P=NS). Complications were few, including pulmonary embolism, sepsis, UTI, HAP, bleeding, and others, had no significant difference between those on tocilizumab and controls in both analysis methods (Supplementary material, and Table 1 footnotes).

Table 1. *The characteristics of COVID-19 patients according to tocilizumab treatment allocation.*

Characteristic	Patients' characteristics segregated according to Tocilizumab allocation					
	All cohort N=1124 (%)			Propensity score matched-patients N=228 (%)		
	Tocilizumab n=142	controls n=982	P *	Tocilizumab n=55	Controls n=173	P *
Age (years)						
Lowest thru 65	70	570	NS	26	101	
66 thru 75	44 (16.8)	218 (83.2)	<0.05	16	44	0.445
76 thru 85	23	155	NS	11	22	
86 thru highest	5	36	NS	2	6	
Gender						
Male	98	616	0.330	38	116	0.778
female	44	365		17	57	
Antivirals						
Favipiravir	108 (14.9)	617 (85.1)	<0.05	35	105	NS
Remdesivir	34	365	NS	10 (18.2)	12 (6.9)	0.015
Colchicine	45 (17.6)	211 (82.4)	<0.05	16	62	0.358
Antibiotics	116 (14.4)	692 (85.6)	<0.05	49	156	0.816
Antifungal	29 (29.3)	70 (70.7)	<0.05	15	30	0.093
Presenting symptoms						
Fever (History)	101 (71.1)	600 (61.1)	<0.05	42	110	NS
Temperature (exam)	142 (100)	959 (97.6)	<0.05	55	173	NS
Chills	81 (57)	458 (46.6)	<0.05	31	75	NS
Sore throat	55 (38.7)	284 (28.9)	<0.05	22	70	NS
Shortness of breath	134 (94.4)	793 (80.8)	<0.05	50	150	NS
Cough	132 (93)	782 (79.7)	<0.05	51	144	NS
Body aches	103 (72.5)	606 (61.7)	<0.05	39	129	NS
Headaches	71 (50)	405 (41.2)	<0.05	26	97	NS
Loss of smell	63 (44.4)	304 (31)	<0.05	29	74	NS
Loss of Taste	63 (44.4)	310 (31.6)	<0.05	27	77	NS
Diarrhea	27 (19)	130 (13.2)	NS	8	19	NS
Rhinorrhea	13 (9.2)	57 (5.8)	NS	4	15	NS
Comorbidities**						
Two or more	90 (63.4)	493 (50.2)	<0.05	40 (72.7)	100 (57.8)	<0.05
Diabetes mellitus	6	57	NS	1	9	
Chronic lung disease	1	11	NS	1	3	
Heart disease	1	14	NS	0	0	0.281##
Hypertension	9	81	NS	1	10	
Malignancy	0	6	NS	0	2	
None	2	29	NS	2	6	
BMI$	134	894	NS	55	173	NS
Tobacco use	18	116	NS	8	21	NS

Characteristic	Patients' characteristics segregated according to Tocilizumab allocation					
	All cohort N=1124 (%)			Propensity score matched-patients N=228 (%)		
	Tocilizumab n=142	controls n=982	P *	Tocilizumab n=55	Controls n=173	P *
Blood oxygen saturation (%)						
>95	10 (7)	223 (22.7)	<0.05	5	27	
91 – 95	42	334	NS	17	59	NS
86 -90	42 (29.6)	208 (21.2)	<0.05	16	44	
80 -85	24	116	NS	9	25	
<79	24 (16.9)	81 (8.2)	<0.05	8	18	
Oxygen delivery method						
RA	4 (2.8)	159 (16.2)	<0.05	1	10	NS
Simple mask	11 (7.7)	138 (14.1)	<0.05	2	10	NS
High flow	13 (9.2)	30 (3.1)	<0.05	5	7	NS
Noninvasive ventilation	13 (9.2)	31 (3.2)	<0.05	6	9	NS
Combined	12 (8.5)	34 (3.5)	<0.05	1	11	NS
Invasive Mechanical Ventilation	11 (7.7)	27 (2.7)	<0.05	6	8	NS
Nonrebreather mask	52 (36.6)	173 (17.6)	<0.05	23 (41.8)	37 (21.4)	<0.05
Nasal Prongs	26 (18.3)	367 (37.4)	<0.05	11 (20.0)	81 (46.8)	<0.05
Radiological score (X-ray and CT)						
No involvement	9	67	NS	2	10	NS
25% Involvement	9	36	NS	5	2	<0.05
>25 – 50% Involvement	52	300	NS	16	54	NS
>50 – 75% Involvement	10 (7)	297 (30.2)	<0.05	28	50	<0.05
>75% Involvement	59 (41.5)	219 (22.3)	<0.05	13 (54.2)	5 (2.8)	<0.05
Laboratory data						
PCT (ng/mL)						
<0.5	57	337	NS	18	78	NS
0.5 – or more	27 (41.5)	106 (23.9)	0.012	12	31	
D-Dimer (ng/mL)	133 (93.6)	913 (92.6)	0.31	49	162	NS
Ferritin ng/ml						
<260	12 (8.6)	154 (17.1)	<0.05	3	15	NS
260 – 1000	47 (33.6)	445 (49.3)	<0.05	20	82	
>1000	81 (57.9)	303 (33.6)	<0.05	32	76	
[&]Complications	3	36	NS	20	16	NS

Number in (brackets) are the proportions for the numbers of the variables and or their subcategory when statistical significance was demonstrated.
*2-sided Significance (P-value) was tested by $\chi 2$, and adjusted by the Bonferroni method. NS: not significant.
[##]2-sided significance calculated for the combined comorbidities by $\chi 2$ test
[$]BMI: body mass index, including nested analysis for categories (see supplementary data).
**Comorbidities: Malignancy; 3 Haemato-malignancy and 3 solid tumors. Chronic lung disease; 8 Bronchial asthma and4 COPD. Chronic heart disease; 8 Coronary disease and 7 chronic heart conditions. DM and HTN largely contributed to the "Multiple comorbidities".
[&]Complications in both All-cohort and PSM populations were statistically not different between the tocilizumab and controls in nested analysis. complications were 39 in all-cohort and 36 in the PSM populations. Events include (pulmonary embolism 8, 0, sepsis 8, 1, HAP3, 0, bleeding 4, 1, cardiac 2, 1, and others 14, 4 respectively). Others; 1 liver injury, 1 coronary syndrome, 1 hyperglycemia, 1 acute kidney injury-hyperkalemia, 1 fibrosis, 1 hypotension, 1 brain dead, 1 barotrauma, and 1 emphysema/ pneumopericardium and 8 transfers to other hospitals/against medical advice, bleeding 2 hemoptyses and 1 GIT. The rest no information

4. Outcomes Analyses

Overall, all-cause mortality was 12.7% (143 patients), and for those who stayed in the ICU the mortality was 54.0% (128 patients). In the all-cohort analysis, there was a significant increase in the proportions of recovery in the controls 39.6%, tocilizumab 9.9% (P<0.000). More patients on tocilizumab significantly were on the needed home oxygen therapy 59.2%, controls 38.6% (P<0.000). Mortality was significantly higher in the tocilizumab than the controls (25.4% vs. 10.9% respectively, P<0.000). The same trends remained with the PSM-adjustment and SIPTW with significantly less recovery and more mortality with the treatment with tocilizumab, but both groups of patients on tocilizumab and comparator did not differ significantly for the need for home oxygen therapy (P=0.945) (Table 2).

Logistic regression analysis demonstrated the tocilizumab was associated with better recovery in the all-cohort patients (B=1.791, Wald $\chi 2$=38.432, Odds=5.998, P=0.000), but negative association with recovery as PSM-matched patients though not significant (Beta=- 0.979, Wald $\chi 2$=1.183, Odds=0.376, P=0.277), and no difference in SIPTW (B=0.383, Wald $\chi 2$=1.077, Odds=1.467, P=0.299). The need for home oxygen therapy was significantly negatively associated with the use of tocilizumab (Beta=- 0.835, Wald $\chi 2$=20.836, Odds=0.434, P=0.000), on PSM-adjusted patients it was not significant (Beta=- 0.410, Wald $\chi 2$=0.306, Odds=0.664, P=0.590), and was not significant in the SIPTW (Beta=0.176, Wald $\chi 2$=267, Odds=1.192, P=0.606). The all-cause mortality was significantly negatively associated with the use of tocilizumab in the all-cohort (Beta=- 1.021, Wald $\chi 2$=21.874, Odds=0.360, P=0.000), however, on the PSM-adjusted patients it was not significant (Beta weight=1.720, Wald $\chi 2$=3.848, Odds=5.584, P=0.050), but in the SIPTW-patients mortality was significantly associated with the use of

tocilizumab (Beta=- 1.071, Wald $\chi2$=4.312, Odds=0.343, P=0.038) (Table 3).

Table 2. *The outcome of using Tocilizumab in the treatment of the COVID-19 patients was analyzed as all-cohort, propensity score adjustment, and inverted probability of treatment weight (IPTW).*

Outcome*	Analysis of the causal effect of Tocilizumab for the participating patients								
	All cohort N=1124			Propensity score- adjusted patients N=228			Stabilized inverse probability of treatment weighing N=228		
	tocilizumab		P	tocilizumab		P	tocilizumab		
	Yes n=134	No n=875		Yes n=55	No n=167		Yes n=55	No n=167	P*
Recovered**	14 (9.9)	389 (39.6)	0.000	7 (12.7)	60 (34.7)	0.002	7 (12.7)	60 (34.7)	0.002
Needs home O_2 therapy	84 (59.2)	379 (38.6)	0.000	27	84	NS	27	84	NS
Death	36 (25.4)	107 (10.9)	0.000	21 (38.2)	23 (13.3)	0.000	21 (38.2)	23 (13.3)	0.000

Number in (brackets) are the proportions for the numbers of the variables and or their subcategory when statistical significance was demonstrated. NS: not significant at 2-sided 0.05 level

*2-sided Significance was tested by Pearson $\chi2$, and adjusted by the Bonferroni method. NS: not significant.

**Recovered: patients with no need for home O2 therapy or symptoms like (fever, headaches, myalgias, loss of taste, loss of smell, chills, and other symptoms that were non-existent before COVID-19.

Table 3. *Analysis of the causal effect of Tocilizumab on the participating patients as depicted by logistic regression analysis.*

Tocilizumab	Recovered			Needs home O_2 therapy			All-cause mortality		
	All-cohort N=1124	PSM N=228	SIPTW N=228	All-cohort N=1124	PSM N=228	SIPTW N=228	All-cohort N=1124	PSM N=228	SIPTW N=228
Beta weight	1.791	- 0.979	0.383	-0.835	-0.410	0.176	-1.021	1.720	-1.071
Wald $\chi2$	38.432	1.183	1.077	20.836	0.306	0.267	21.874	3.848	4.312
Exp (B)	5.998	0.376	1.467	0.434	0.664	1.192	0.360	5.584	0.343
Significance (P)*	0.000	0.277	0.299	0.000	0.590	0.606	0.000	0.050	0.038

*2-sided Significance. PSM: a propensity score-matched patients. SIPTM: the stabilized probability of treatment weight

5. Discussion

All-cohort patients had few imbalanced characteristics for tocilizumab and the controls, but were balanced in the PS-adjusted patients: the age categories (P=0.445), gender (P=0.778), colchicine (P=0.358), antibiotics (P=0.816), antifungals (P=0.093), presenting symptoms and the measured temperature (P=NS), tobacco use (P 0.641), blood oxygen saturation (P 0.675), PCT levels (P=0.225), D-Dimer (P=0.065), ferritin categories (P=0.176) and a few in-hospital complications (P=0.831). Other characteristics were PS-adjusted but showed some imbalance in the sub-characteristic like remdesivir, its use was associated more with the use of tocilizumab (P=0.015) though it did not have a significant effect difference [16]. "Two-or-more comorbidities" (Table 1) were more in tocilizumab (P<0.05) but the rest were well-balance (P=NS). The oxygen delivery method group, the nonrebreather mask and nasal prongs delivery methods, the characteristics remained significantly imbalanced (P<0.05). The radiological scores:>50% - 75% and>75% lung involvement were imbalanced (P<0.05) and remained so with PS-adjustment, nonetheless, the imbalances were modest (P>0.01) (Table 1).

The clinical recovery (Table 2 footnotes, and supplementary materials for definition) was significantly less in the tocilizumab-treated patients for the all-cohort (P=0.000), PSM-adjusted (P=0.002) and the SIPTW patients (P=0.002), similar to other previous work for a similar endpoint [17], this finding was further verified by logistic regression (Table 3), and unlike other studies that showed low-dose tocilizumab was associated with a rapid improvement in clinical and laboratory measures in hospitalized patients with COVID-19 [18]. Nonetheless, in our study, tocilizumab dosing regimens differed, this would have affected an accurate estimation of the tocilizumab casual effect and outcomes interpretations. Physicians tend to use tocilizumab when there was a pressing clinical and or laboratory deterioration (supplementary data), similar to what was reported in the literature for the indications and doses [19]. Similarly, logistic regression analysis showed that recovery was not associated with the tocilizumab-treated patients in the all-cohort (Beta=1.791, Wald $\chi2$=38.432, Odds=5.998, P=000), however, it was not different from the controls in PSM (Beta=- 0.979, Wald $\chi2$=1.183, Odds=0.376, P=0.277) and SIPTW analysis (Beta=0.383, Wald $\chi2$=1.077, Odds=1.467, P=0.299), see (Table 3).

The need for home oxygen therapy was not considered as a useful composite endpoint in the studies we reviewed, we think that using "the need for home oxygen therapy" as an endpoint is important to be included, and may be used as a composite clinical improvement indicator for the progress of COVID-19 patients health condition. The need for home oxygen therapy was significantly more in patients who were treated with tocilizumab in all-cohort patients (N=84, 59.2% versus N=379, 38.6%, P=0.000), however with PSM there was no difference (P=0.945), and for the SIPTW (P=0.945). Logistic regression analysis demonstrated a significant negative effect with the use of tocilizumab on the need for home oxygen (Beta=- 0.835, Wald $\chi2$=20.836, Odds=0.434, P=000), but no difference with PSM (P=0.590) and SIPTW (P=0.606) analyses (Table 3)., hitherto, there is no evidence

that tocilizumab provides an additional benefit in preventing the need for home oxygen in patients with COVID-19 patients.

Our study demonstrated an association of tocilizumab use to mortality: all-cause mortality was higher in the tocilizumab-treated patients for the all-cohort patients (P=0.000), and the difference remained significant in the PSM patients (P=0.000) and the SIPTW patients (P=0.000). In this regard, the findings were concurred to an extent from logistic regression analysis (Table 3), where tocilizumab was associated with mortality in the all-cohort analysis (Beta=-1.021, Wald $\chi2$=21.874, Odds=0.360, P=0.000), this was in line with SIPTW (Beta=- 1.071, Wald $\chi2$=4.323, Odds=0.343, P=0.038), but borderline in PSM analysis (Beta=1.720, Wald $\chi2$=3.848, Odds=5.584, P=0.050). Many studies with a focus on mortality had inconsistent results; in a cohort of 21 patients, tocilizumab administration did not reduce ICU admission or mortality rate. [20]. A systemic review and meta-analysis of retrospective studies and a metanalysis of a randomized control trial demonstrated that tocilizumab did not have a clear mortality benefit over controls in the treatment of patients with moderately ill hospitalized patients, severely ill patients, and patients with various clinical presentations [21-23], moreover, a propensity score analysis study of 96 patients with COVID-19 pneumonia, tocilizumab did not improve the overall survival (P=0.338). [24]. A focus on elevated IL-6 levels in COVID-19 pneumonia patients, levels correlated with mortality, but it did not change with tocilizumab administration [25].

On the other hand, in an observational study, patients with COVID-19 requiring ICU support who received tocilizumab had reduced mortality [26], nonetheless**,** a meta-analysis of observational and randomized control (RCT) presented contradictory results; in the observational arm tocilizumab was associated with a reduced mortality rate in both severe and critically ill patients, but the meta-analysis of the RCT arm (excluding the RECOVERY study) failed to find any difference between a standard therapy plus tocilizumab versus standard therapy alone [27]. In a multicenter cohort study that included 3924 critically ill patients with COVID-19, the risk of in-hospital mortality was found to be lower in patients treated with tocilizumab in the first two days of ICU admission [28]. CRP levels were used as an indicator in an observed 1229 patients, tocilizumab was associated with a lower risk of death or ICU admission or death **i**n patients with higher levels [29]. Fifty percent of 154 mechanically ventilated COVID-19 patients received tocilizumab and were followed up to a median of 47 days (range, 28–67), tocilizumab was associated with lower mortality despite higher superinfection occurrence [30]. Studies that support mortality benefit came mostly from unadjusted observational studies.

6. Conclusion

A previous meta-analysis of RCT demonstrated no benefit and more mortality with the use of tocilizumab. Now, the administration of tocilizumab to COVID-19 patients was associated with less recovery and increased mortality and was not associated with a change in the need for home oxygen therapy. Our study employed PSM and SIPTW analyses, both methods are robust and came in line with other previous RCTs and a PSM adjusted study that we found.

Key Points

Tocilizumab was not associated with a better recovery, improved rates for home oxygen use on discharge and did not improve mortality in this PSM and SIPTW study.

Conflict of Interest

The authors declare that they have no competing interests.

Ethics

The study was approved by the IRB of the three participating hospitals.

Patient Consent

Not applicable (observational study).

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