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The Egyptian Journal of Bronchology (2023) 17:46
https://doi.org/10.1186/s43168-023-00220-7

The Egyptian Journal of Bronchology

RESEARCH Open Access

Safety and efficacy of tocilizumab in critically ill patients with COVID-19: an observational study

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Abstract

Background Since the coronavirus disease 2019 (COVID-19) outbreak has rapidly propagated with a high mortality rate, it is currently considered a global emergency. Worldwide, the number of patients with severe acute respiratory syndrome caused by coronavirus 2 is steadily rising. Pneumonia, severe symptoms of acute respiratory distress syndrome (ARDS), and multiple organ failure can all occur in COVID-19 patients.

Aim of the work To compare the clinical symptoms and inflammatory markers before and after the administration of 2 doses of tocilizumab, acknowledging that the second dose is given within 24–48 h following the first dose.

Patients and methods Baseline CBC with differential, liver function tests, kidney function tests, D dimer, serum ferritin, and CRP were withdrawn. Two doses of tocilizumab were given over 2 days; the first dose was 8 mg/kg diluted in 100 cc saline 0.9% administered over 1 h while the second dose (4 mg/kg diluted in 100 cc saline 0.9%) was given after 24 h. Follow-up inflammatory markers were withdrawn after 3 days following the second dose of tocilizumab. Clinical symptoms were evaluated 48 h following the second dosage of tocilizumab. Oxygen therapy was evaluated on the second and the thirtieth days following tocilizumab administration.

Results The administration of tocilizumab highly and significantly improves some clinical symptoms (bony aches, fatigue, fever), oxygen therapy, and PO_2/FiO_2 ratio. Also, its administration showed no significant effect on the inflammatory markers other than CRP which showed a marked increase. Tocilizumab treatment resulted in worsened expectoration. Tocilizumab showed neither effect on patients' fate and mortality nor on hospital stay. A mean age of 61 was statistically and highly significant in increased patient mortality. Renal impairment significantly affected the length of hospital stay. The effect of timing of tocilizumab administration on patients' fate and mortality showed non-statistically significant improvement when given from day 6 to day 10 since the onset of symptoms.

Conclusion The administration of tocilizumab highly and significantly improves clinical symptoms, oxygen therapy, and PO_2/FiO_2 ratio, with no significant effect on inflammatory markers other than CRP which showed a marked increase, which may be attributed to early withdrawal of inflammatory markers. Tocilizumab shows neither the effect on patients' fate and mortality nor on hospital stay although the mean age of 61 was statistically highly significant on increased patients' mortality and renal impairment significantly affected length of hospital stay.

Keywords Safety efficacy, Tocilizumab critically, COVID-19, Observational study

Introduction

Coronavirus disease 2019 (COVID-19) emerged in China in December 2019 and rapidly led to a public health emergency [1, 2]. Acute respiratory distress syndrome can develop in severe and critical cases of COVID-19,

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which affects 14% and 5% of patients, respectively [3, 4]. One of the main reasons of death in individuals with COVID-19 is respiratory failure [5, 6].

Currently, it is crucial to look into the causes of death and accelerate the development of novel treatments for severe COVID-19. According to the study of the biopsy samples performed at autopsy, increased alveolar exudate brought on by an inflammatory cytokine storm and an abnormal host immune response likely obstruct alveolar gas exchange. This contributes to the significant mortality of COVID-19 patients. Our research has shown that inflammatory monocytes and pathogenic T lymphocytes produce substantial amounts of interleukin 6, which could potentially prevent an inflammatory storm from occurring [7].

In December 2019, COVID-19 was first identified in Wuhan, China. The disease's principal and well-known symptoms include fever, respiratory distress, and the inability to breathe on one's own, all of which can result in pneumonia.

However, other symptoms, such as various neurological symptoms and diarrhea, may also be considered clinical indicators of this illness. Furthermore, it has been discovered that high levels of cytokine release in critical patients, which ultimately culminates in CRS (cytokine release syndrome) more often known as cytokine storm, are significantly related to the severity and fatality of the disease.

The progression of the illness from severe to very serious is strongly correlated with these cytokine storms. Cytokines are tiny chemical messengers, specifically designated for immunogenic response, and can cause both adaptive and innate immune responses. Interferons, interleukins, growth factors, TNF or tumor necrosis factors, chemokines, and other tiny molecules are among them. Surprisingly, the link between CRS, also known as a cytokine storm, and high morbidity has been found in earlier coronavirus infections caused by various viruses, including SARS-CoV and MERS-CoV [5].

The classical IL-6 signal is restricted to cells (macrophages, neutrophils, T cells, etc.) that express the IL-6R and contribute significantly to the low level of IL-6. Initiating downstream pathways, gp130 homologous dimerization is brought on by the interaction of IL-6 and cell-related IL-6R. However, because gp130 is so common, the IL-6 signal spreads when the level of IL-6 rises. Tocilizumab can suppress both trans and classical signals by binding to cell-related IL-6R and sIL-6R. As a result, it can prevent CRS [8].

A recombinant monoclonal antibody of the IgG1 subclass, tocilizumab, is directed against human IL-6R. Tocilizumab selectively binds soluble and membrane-bound IL-6 receptors, inhibiting both types of receptors' ability to transmit signals. It has been licensed for the treatment of Crohn's disease, systemic juvenile idiopathic arthritis, and rheumatoid arthritis. It is important to note that tocilizumab is efficient in the treatment of patients with severe CRS [9].

Inspiring clinical outcomes were also shown with the use of tocilizumab, which blocks IL-6 receptors, including a rapid recovery to normal temperature and enhanced respiratory function. As a result, we propose that tocilizumab is a successful therapy for COVID-19 patients who have severe disease, as it can reduce mortality and calm the inflammatory storm [7].

Aim of the work

To compare the clinical symptoms (mMRC dyspnea score), oxygen therapy, TLC and lymphocytic count, and inflammatory markers (CRP, serum ferritin, D-dimer) before and after the administration of 2 doses of tocilizumab noting that the second dose is given within 24–48 h following the first dose on 50 patients admitted to Ain Shams Isolation University Hospital et al.-Obour, Ain Shams Geriatrics Isolation Hospital and Ain Shams Isolation Field Hospital from May 1, 2020, to January 1, 2022.

Patients and methods

This is a prospective cross-sectional observational study to compare the clinical symptoms (mMRC dyspnea score), oxygen therapy, TLC and lymphocytic count, and inflammatory markers (CRP, serum ferritin, D-dimer) before and after the administration of 2 doses of tocilizumab noting that the second dose is given within 24–48 h following the first dose on 50 patients admitted to Ain Shams Isolation University Hospital et al.-Obour, Ain Shams Geriatrics Isolation Hospital and Ain Shams Isolation Field Hospital from May 1, 2020, to January 1, 2022.

Inclusion criteria

- Positive PCR for COVID-19 [10], oxygen saturation on room air < 90% or drop of oxygen saturation on room air > 3% during 24 h [10], radiological doubling of heterogenous opacities in chest X-ray or ground glass opacities in CT-chest, a semiquantitative CT severity scoring was done using "25-point CT severity score" by Pan et al. [11].

Exclusion criteria

- Unconfirmed cases by PCR for COVID-19 [10], confirmed cases with no symptoms or CT findings [12]. confirmed cases with oxygen saturation > 94%

[10], active bacterial infection (leucocytosis with absolute neutrophilia, laboratory positive procalcitonin or radiological signs of bacterial infection as lobar consolidation), active tuberculosis, fungal infection [10], liver enzymes > 5 folds, absolute neutrophilic count < 500 cell/mm^3, platelets < 50,000 cell/mm^3 [13], and patient with e-GFR ≤ 30 ml/min

Ethical consideration This study was done after the approval of the research ethical committee, Faculty of Medicine, Ain Shams University, on patients diagnosed with COVID-19 infection "PCR positive for SARS COV 2 "who were admitted to Ain Shams Isolation University Hospital et al.-Obour, Ain Shams Geriatrics Isolation Hospital and Ain Shams Isolation Field Hospital, in the period from May 1, 2020, to January 1, 2022.

Study intervention All patients received a tocilizumab dose of 8 mg/kg diluted in 100-ml isotonic saline infused over 1 h followed by a second dose of 4 m/kg diluted in 100 isotonic saline infused over 1 h within 24–48 h from the first dose.

Clinical symptoms Inflammatory markers and oxygenation were assessed after 48 h of administration of tocilizumab and along the course of 30 days from onset of symptoms [14].

CT severity scoring It was calculated per each of the 5 lobes considering the extent of anatomic involvement, as follows [15]: The 3 lung lobes on the right and 2 lobes on the left were individually assessed, and the percentage involvement of the lobe was noted based on visual assessment. Visual severity scoring of CT chest was classified as a score of 1 (< 5% area involved), a score of 2 (5–25% area involved), a score of 3 (25–50% area involved), a score of 4 (50–75% area involved), and a score of 5 (> 75% area involved), making the total score 25. A CT severity score was assigned out of 25 based on the percentage area involved in each of the 5 lobes. The total CT score is measured by the sum of the individual lobar scores and can range from 0 (no involvement) to 25 (maximum involvement), when all the five lobes show more than 75% involvement. The sum of individual lobar scores indicates the overall CT severity grading as < 8 mild (grade 1), 9–15 moderate (grade 2), and > 15 severe (grade 3) [11, 15].

Treatment protocol These are as follows: broad-spectrum antibiotics, pulse steroids: 1–2 mg/kg/day methylprednisolone, prophylactic anticoagulation, supplemental vitamin C and zinc, and antiviral in the Viremic stage. Tocilizumab was given as an add-on therapy after methylprednisolone if no improvement in oxygenation on steroids. This treatment protocol follows the Ain Shams University Hospital management protocol [16].

Dosage adjustments *Renal impairment*: mild-to-moderate (eGFR ≥ 30 mL/min): no dosage adjustment required and severe (eGFR < 30 mL/min): not studied.

Liver enzyme abnormalities: > 1 to ≤ 3x: decrease tocilizumab dose to 4 mg/kg or postpone dose and restart until ALT/AST gets normal.

> 3 to ≤ 5x: postpone dose until < 3 × and apply recommendations above for > 1 to ≤ 3x.

Persistent increase > 3x: stop tocilizumab

> 5x: stop therapy

Neutropenia: ANC > 1000 cells/mm^3: maintain dose, ANC 500–1000 cells/mm^3

IV: resume at 4 mg/kg and increase to 8 mg/kg as clinically appropriate and ANC < 500 cell/mm^3: discontinue therapy

Thrombocytopenia: 50,000–10,000 cells/mm^3, hold dose, resume when platelet count > 100,000 cells/mm^3, < 50,000 cells/mm^3, and discontinue therapy.

Patient assessment: clinical symptoms (ordinal scale for clinical improvement), inflammatory markers, and oxygenation will be assessed after 48 h of administration of tocilizumab and along the course of 30 days from the onset of symptoms.

Patient safety consideration: informed consent, drug sensitivity test, and dosage adjustments according to the patient's laboratory findings

Statistical analysis

Data was collected, revised, coded, and entered into the Statistical Package for Social Science (IBM SPSS) version 23 "manufactured in Hong Kong, China." The quantitative data were presented as the mean, standard deviations, and ranges when parametric and median, and interquartile range (IQR) when data was found non-parametric. Also, qualitative variables were presented as numbers and percentages. The comparison between groups regarding qualitative data was done by using chi-square test and/or Fisher's exact test when the expected

count in any cell was found less than 5. The comparison between more than two groups regarding quantitative data and parametric distribution was done by using the one-way ANOVA test while non-parametric distribution was done by using *Kruskall-Wallis* test. The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the *P* value was considered significant as the following: (*P* value > 0.05: nonsignificant (NS), *P* value < 0.05: significant (S) and *P* value < 0.01, highly significant (HS).

Results

Table 1 shows the highly statistical significance of improvement of expectoration, bony aches, fatigue, and fever after administration of tocilizumab but however shows no statistical significance of improvement of dyspnoea, cough, loss of taste, anosmia, and sore throat.

Table 2 shows the high statistical significance of tocilizumab administration on oxygen therapy and PO_2/FiO_2 ratio after 48 h.

Table 3 shows a statistical significance of renal impairment on hospital stay while shows no statistical significance of age, diabetes, hypertension, hepatic impairment, cardiac, and pulmonary comorbidities on hospital stay.

Table 4 shows no statistical significance of comorbidities on patients' outcome.

Table 5 shows Course of patients; oxygen therapy after administration of tocilizumab on day 2 and day 30.

Discussion

This study compares clinical symptoms (MMRC dyspnea score), oxygen therapy, TLC and lymphocytic count, and inflammatory markers (CRP, serum ferritin, D-dimer) before and after the administration of 2 doses of tocilizumab noting that the second dose is given within 24–48 h from the first dose.

The new infectious disease COVID-19 has a complex etiology. The cytokine release syndrome (CRS) appears to play a significant pathogenic role in severe SARS-CoV-2 infections, according to laboratory data. Interleukin-6 (IL-6) is the most significant proinflammatory cytokine in CRS, despite the fact that it has been found to be a poor prognostic indicator [17, 18]. Promising COVID-19 therapy options include anti-IL-6 medications [19, 20]. A humanized monoclonal antibody called tocilizumab has been studied for its effectiveness in treating severe COVID-19 because it can target the IL-6 receptor in both its membrane-bound and soluble versions [21–26].

Among the 50 patients included in this study, it was found that 32 (64%) cases were males while 18 cases were females (36%), their ages ranged from 28 to 75 years with a mean of 53 years. Twenty-five cases (50%) were smokers while 7 cases (14%) were exposed to biomass fuel and

Table 1 Effect of tocilizumab administration on symptoms

	Dyspnea			**Total**	***P* value***
	3.00		**4.00**		
Dyspnea (MMRC)	**3.00**	0	2	2	0.29 NS
	4.00	6	42	48	
Total	6		44	50	
	Cough after			**Total**	***P* value***
	No		**Yes**		
Cough before	**No**	2	7	9	1.00 NS
	Yes	6	35	41	
Total	8		42	50	
	Expectoration after			**Total**	***P* value***
	No		**Yes**		
Expectoration before	**No**	34	12	46	< 0.001 HS
	Yes	0	4	4	
Total	34		16	50	
	Bony aches after			**Total**	***P* value***
	No		**Yes**		
Bony aches before	**No**	2	3	5	0.01 HS
	Yes	14	31	45	
Total	16		34	50	
	Fatigue after			**Total**	***P* value***
	No		**Yes**		
Fatigue before	**No**	2	3	5	0.01 HS
	Yes	15	30	45	
Total	17		33	50	
	Loss of taste after			**Total**	***P* value***
	No		**Yes**		
Loss of taste before	**No**	41	4	45	0.13 NS
	Yes	0	5	5	
Total	41		9	50	
	Anosmia after			**Total**	***P* value***
	No		**Yes**		
Anosmia before	**No**	40	4	44	0.13 NS
	Yes	0	6	6	
Total	40		10	50	
	Sore throat after			**Total**	***P* value***
	No		**Yes**		
Sore throat before	**No**	23	7	30	0.80 NS
	Yes	9	11	20	
Total	32		18	50	
	Fever after			**Total**	***P* value***
	No		**Yes**		
Fever before	**No**	12	6	18	0.01 HS
	Yes	21	11	32	
Total	33		17	50	

* McNemar's test

Table 2 Effect of tocilizumab on oxygen therapy and PO_2/FiO_2 ratio

		O_2 therapy after 48 h							Total	*P* value*
		Nasal cannula (3–6L)	Nasal cannula (< 3L)	NRHF	Face mask (< = 10L)	CPAP	MV	Died		
O2 therapy before	**NRHF**	16	0	0	8	7	4	3	38	< 0.001 HS
	Nasal Cannula	0	4	2	0	1	1	0	8	
	CPAP	1	0	0	0	0	1	2	4	
Total		17	4	2	8	8	6	5	50	
PO_2/FiO_2 after 48 h										
		< 200		**> 200**		**Total**		***P* value***		
PO_2/FiO_2 before	**< 200**	25		17		42		0.01 HS		
	> 200	4		4		8				
Total		29		21		50				

* Marginal homogeneity test

Table 3 Effect of Age and comorbidities on hospital stay

Age		**Pearson's correlation**		**Hospital stay (days)**	
				0.15	
		***P* value**		**0.29 NS**	
		Hospital stay (days)		***t*[a]**	***P* value**
		Mean	**SD**		
Diabetic	**No**	18.78	5.27	0.75	0.46 NS
	Yes	17.74	4.52		
Hypertensive	**No**	18.81	4.78	0.73	0.47 NS
	Yes	17.79	4.95		
Liver cirrhosis or HCV	**No**	18.61	4.94	1.58	0.12 NS
	Yes	15.33	3.14		
Chronic kidney disease	**No**	18.90	4.80	2.39	0.02 S
	Yes	14.62	3.50		
Ischemic heart disease	**No**	18.69	5.15	1.31	0.20 NS
	Yes	16.55	3.30		
Chronic pulmonary disease	**No**	18.70	5.07	1.41	0.16 NS
	Yes	16.30	3.43		

[a] Student *t* test

5 cases were bird breeders (10%). Regarding the distribution of comorbidities, 27 cases (54%) were diabetic, 29 cases (58%) were hypertensive, 8 cases (16%) had chronic renal impairment, 6 cases (12%) had liver cirrhosis and HCV, and 11 cases (22%) had ischemic heart disease while 10 cases (20%) had chronic pulmonary diseases subdivided into 8 COPD cases (16%) and 2 cases interstitial lung diseases (4%).

This is nearly in agreement with Hermine et al., (2021) who studied 63 cases in a group receiving tocilizumab; of the 63 patients, 44 were males (70%) while 19 were females (30%) with a mean age of 63 years [27].

A semiquantitative CT severity scoring was done using a "25-point CT severity score" by Pan et al. [11]. CT severity was graded as < 8 mild, 9–15 moderate, and > 15 severe [11, 15]. Among the study patients, 11 (22%) patients had mild severity (grade 1), 25 (50%) patients had moderate severity (grade 2), and 14 (28%) patients had grade 3 severity.

Differing in number of smokers, who contribute only 6 cases (10%), and distribution of comorbidities, 20 cases (33%) were diabetic, 20 cases (33%) were cardiac, and 5 cases (8%) had renal impairment while 8 cases (13%) had pulmonary diseases.

Regarding the main presenting symptoms, 100% of the cases presented with dyspnea differing in mMRC score (2 cases (4%) were mMRC 3 while 48 cases (96%) were mMRC 4), 41 cases (82%) had cough, 4 cases (8%) had expectoration, 45 cases (90%) had bony aches and fatigue, 5 cases (10%) had loss of taste while 6 cases (12%) were anosmic, and 20 cases (40%) had sore throat while 32 cases (64%) were feverish.

This is nearly in agreement with Tomasiewicz et al., (2021) who studied 28 cases receiving tocilizumab, where 86% of cases presented with dyspnea, 89% had cough, 11% were anosmic, and 89% were feverish, however differing in bony aches which contributed to only 29% of the cases [28].

Regarding the range of inflammatory markers among patients' labs, TLC ranged from 2 to 20 with a mean of 13, absolute lymphocytic count of 0.10–3 with a mean of 0.68, D-dimer from 1.2–4 with a mean of 3.02, CRP from 41 to 190 with a mean of 94 while serum ferritin ranged from 550 to 2000 with a mean of 1083.

Table 4 Effect of comorbidities on patients' outcome

		Outcome				X^{2*}	*P* value
		Died		Discharged			
		N	%	*N*	%		
Diabetic	**No**	4	17.4%	19	82.6%	1.02	0.31 NS
	Yes	8	29.6%	19	70.4%		
Hypertensive	**No**	3	14.3%	18	85.7%	1.87	0.17 NS
	Yes	9	31.0%	20	69.0%		
Liver cirrhosis or HCV	**No**	10	22.7%	34	77.3%	0.33 FE	0.62 NS
	Yes	2	33.3%	4	66.7%		
Chronic kidney disease	**No**	9	21.4%	33	78.6%	0.95	0.33 NS
	Yes	3	37.5%	5	62.5%		
Ischemic heart disease	**No**	7	17.9%	32	82.1%	3.56	0.06 NS
	Yes	5	45.5%	6	54.5%		
Chronic pulmonary disease	**No**	8	20.0%	32	80.0%	1.75	0.19 NS
	Yes	4	40.0%	6	60.0%		
Smoking	**No**	4	16.0%	21	84.0%	1.754	0.185NS
	Yes	8	32.0%	17	68.0%		

* Chi-square test (*FE* Fisher's exact test)

Table 5 Course of patients, oxygen therapy after administration of tocilizumab on day 2 and day 30

	O_2 therapy before tocilizumab	O_2 therapy after tocilizumab on day 2	Follow-up oxygen therapy/outcome after on day 30
O_2 therapy (*N* = 50)	**NRHF (*N* = 38)**	**Nasal cannula (3–6L) (*N* = 16)**	**Discharged on room air (*N* = 9)**
			Discharged on domiciliary O_2 (*N* = 7)
		Face mask (≥ 10L) (*N* = 8)	**Died (*N* = 1)**
			MV (*N* = 2)
			Discharged on room air (*N* = 2)
			Discharged on domiciliary O_2 (*N* = 3)
		CPAP (*N* = 7)	**MV (*N* = 4)**
			Discharged on domiciliary O_2 (*N* = 3)
		MV (*N* = 4)	**Died (*N* = 4)**
		Died (*N* = 3)	
	Nasal cannula (3–6L) (*N* = 8)	**Nasal cannula (< 3L) (*N* = 4)**	**Discharged on room air (*N* = 3)**
			Discharged on domiciliary O_2 (*N* = 1)
		NRHF (*N* = 2)	**MV (*N* = 1)**
			Discharged on domiciliary O_2 (*N* = 1)
		CPAP (*N* = 1)	**MV (*N* = 1)**
		MV (*N* = 1)	**Died (*N* = 1)**
	CPAP (*N* = 4)	**Nasal cannula (3–6L) (*N* = 1)**	**Discharged on room air (*N* = 1)**
		MV (*N* = 1)	**Died (*N* = 1)**
		Died (*N* = 2)	

The range of inflammatory markers is in agreement with Hermine et al., (2021) who studied 63 cases in a group receiving tocilizumab, D-dimer ranged from 524 to 1380 while serum ferritin from 424 to 2484 but differs in TLC which ranged from 3.9 to 7.5, absolute lymphocytic count from 0.7 to 1.4, and CRP from 74.5 to 219 [27].

Of the 50 cases, 38 (76%) patients achieved oxygen saturation > 94% on non-rebreathing high-flow oxygen masks, 8 patients (16%) were on nasal cannula 3–6 L while 4 patients (8%) were on CPAP, the PO_2/FiO_2 ratio of the patients was < 200 for 42 cases (84%) and > 200 for 8 cases (16%). After administration of tocilizumab, 2 (4.4%) patients achieved oxygen saturation > 94% on a non-rebreathing high-flow oxygen mask, 17 patients (37.8%) were on the nasal cannula 3–6 L, 4 patients (8.9%) on the nasal cannula < 3L while 8 patients (17.8%) were on CPAP and 6 patients (13.3%) were mechanically ventilated. The PO_2/FiO_2 ratio of the patients was < 200 for 29 cases (58%) and > 200 for 21 cases (42%).

This is not the same as Rodríguez-Baño et al., (2021) who studied 344 patients, 82% were on the nasal cannula/mask, 13% were on non-rebreathing high-flow mask, and 0.6% were on CPAP [29]. The PO_2/FiO_2 ratio of cases studied by Gupta et al., (2021) were 8.5% > 200 and 47% < 200 [30].

After administration of tocilizumab for 48 h, clinical symptoms were reassessed, bony aches (decreased from 45 to 34 cases) fatigue (from 45 to 33), and fever (32 to 17) showed marked improvement after administration of tocilizumab which is statistically highly significant, while cases experienced expectoration increased from 4 to 16 cases which is statistically highly significant. This is nearly the same as Wang et al., [31] who studied two groups (the tocilizumab receiving group consisting of 34 patients and the control group consisting of 31 patients), the percentage of cases experiencing bony aches and fatigue in the control group was 16% while only 8% in the tocilizumab group. Differing in the percentage of cases experienced fever which contributed to 16% in the control group while 23% of cases in the tocilizumab group were feverish and the percentage of cases who had expectoration was almost the same in both groups [31].

Inflammatory markers were sampled after 3 days from administration of tocilizumab. There was no statistically significant change in TLC, lymphocytes, D-dimer, and serum ferritin after tocilizumab while CRP showed statistically significant relation to tocilizumab as the mean CRP level increased from 94 to 117 ($P=0.003$). There is no statistically significant change in TLC, lymphocytes, D-dimer, serum ferritin, serum creat, AST, and ALT on patients' mortality with statistical significance of CRP on patients' fate which gives 83% sensitivity and 50% specificity to predict mortality at best cutoff = 83.5 which is nearly in agreement with the study Amin et al., (2021) which concluded that tocilizumab-induced change in dimers and TLC count was not substantial, differing in CRP levels which showed marked reduction after tocilizumab [32].

Tocilizumab administration was found to be highly statistically significant in the improvement of oxygen therapy and PO_2/FiO_2 ratio which is in agreement with Wang et al., (2021) who found that tocilizumab can improve oxygenation and symptoms and reduce disease worsening with an acceptable side effect profile [31], but not the same as study Salvarani et al., (2021) who found that the administration of tocilizumab in patients with COVID-19 pneumonia and a PaO_2/FiO_2 ratio between 200 and 300 mmHg did not reduce the risk of clinical worsening [33]. In our study, tocilizumab did not affect patients' fate and mortality which is in agreement with the study Hermine et al., (2021) who found that tocilizumab did not reduce the risk of mechanical ventilation and mortality [27].

We studied the effect of timing of tocilizumab administration on both patients' mortality and outcome, but it showed no statistically significant relation ($P=0.80$, 0.27 respectively), although it was noted that 29 cases who were discharged either on room air or domiciliary oxygen received tocilizumab from day 6 to 10 since onset of symptoms which is nearly in agreement with study Gupta et al., (2021) which concluded that among critically ill patients, the risk of in-hospital mortality was lower in patients treated early with tocilizumab in the first 7 days of admission compared with patients whose treatment did not include early use of tocilizumab [30].

Other factors may affect patients' mortality; we studied the effect of age and different comorbidities on mortality rate, and our study showed that only age had a highly statistically significant relation to mortality ($P=0.002$) with a mean age of 50 years for patients who were discharged while the mean age for patients who died was 63, which is in agreement with Burlacu et al., (2021) who showed that age above 72 years was the only independent factor associated with death, yielding a 15-fold superior risk, but in contrast to our study, it showed that respiratory diseases such as chronic obstructive pulmonary disease were also associated with an increased risk of death in COVID-19 [34].

Regarding the hospital stay of the patients, we studied the effect of age and comorbidities on the length of hospital stay, and only chronic kidney disease showed statistical significance ($P=0.02$) which is nearly in agreement with Al-Baadani et al. [35] who studied the relation between hospital stay and different comorbidities (diabetes, hypertension, chronic liver diseases, chronic kidney diseases, asthma) and found no statistical significance.

Conclusion

The administration of tocilizumab highly significantly improves clinical symptoms, oxygen therapy, and PO_2/FiO_2 ratio, with no significant effect on inflammatory markers other than CRP which showed a marked increase, which may be attributed to early withdrawal of inflammatory markers. Tocilizumab shows neither effect on patients' fate and mortality nor on hospital stay although the mean age of 63 was statistically highly significant on increased patients' mortality and renal impairment significantly affected length of hospital stay. We studied the effect of the timing of tocilizumab administration on patients' fate and mortality which showed no statistically significant improvement when given from day 6 to day 10 since the onset of symptoms which may be due to a small sample size.

Abbreviations

COVID-19	Coronavirus 19
ARDS	Acute respiratory distress syndrome
CBC	Complete blood picture
CRP	C-reactive protein
PO_2	Partial pressure of oxygen
FiO_2	Fraction of inspired oxygen
CRS	Cytokine release syndrome
TNF	Tumor necrosis factor
SARS-COV	Severe acute respiratory syndrome coronavirus
MERS-COV	Middle East respiratory syndrome coronavirus
IL-6	Interleukin-6
IL-6R	Interleukin 6 receptor
GP130	Glycoprotein 130
SIL-6R	Soluble interleukin 6
IgG1	Immunoglobulin G 1
MMRC	Modified Medical Research Council
TLC	Total leucocyte count
PCR	Polymerase chain reaction
e-GFR	Estimated glomerular filtration rate
ANC	Absolute neutrophil count
COPD	Chronic obstructive pulmonary disease
ILD	Interstitial lung disease
HCV	Hepatitis C virus
NRHF	Non-rebreathing HiFlow
CPAP	Continuous positive airway pressure
MV	Mechanical ventilation
S. ferritin	Serum ferritin

Acknowledgements

The authors would like to acknowledge all those who shared in data acquisition and made medical records available for us to revise.

Authors' contributions

GA collected the patient's data. GA wrote the initial manuscript. HM revised the manuscript. HM and GA performed the computations and verified the analytical methods. KW revised the manuscript. KW, HM, and GA were major contributors in writing the manuscript, and they supervised and reviewed the data collection and statistical analysis. The authors read and approved the final manuscript. HM published the final manuscript.

Funding

Nil.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author, HM, upon reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the ethics committee of Ain Shams University, Faculty of Medicine, ethical approval no. FMASU MS512/2021. The subject participant provided written consent.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Received: 12 March 2023 Accepted: 18 August 2023
Published online: 01 September 2023

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