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Original Article

A single-center experience in use of tocilizumab in COVID-19 pneumonia in India

Aditya Joshi [a], *Krishna Kumar M* [a], *Abhishek Kumar* [b], *Ranjith K. Nair* [c], *Jasdeep Singh* [d], *Ritwik Chakrabarti* [e], *Rajan Kapoor* [c,*]

[a] *Assistant Professor (Anaesthesia), Command Hospital (Eastern Command), Kolkata, India*
[b] *Associate Professor (Medicine), Command Hospital (Eastern Command), Kolkata, India*
[c] *Professor (Medicine), Command Hospital (Eastern Command), Kolkata, India*
[d] *Assistant Professor (Pathology), Command Hospital (Eastern Command), Kolkata, India*
[e] *Assistant Professor (Radiology), Command Hospital (Eastern Command), Kolkata, India*

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ABSTRACT

Background: IL-6 receptor antagonist tocilizumab (TCZ) has been used in several reported studies in the treatment of COVID-19 pneumonia and pieces of evidence are still emerging.
Methods: All patients with COVID-19 pneumonia showing features of hyperinflammatory syndrome receiving TCZ at a tertiary care center in India were included in the study and a retrospective descriptive analysis was done.
Results: Between May 2020 to August 2020, 21 patients received TCZ out of which 13 survived and 8 died. All non-survivors had longer duration (median 12 days, minimum 9, maximum 15 days compared to median 6 days, minimum 3 and maximum 14 days in survivors) of symptoms and severe disease requiring mechanical ventilation at the time of TCZ administration. Among survivors, 8 patients had severe disease, 3 had moderate disease, and 2 patients had mild disease. Six out of 8 (75%) among non-survivors and 8 out of 13 (62%) among survivors had preexisting medical comorbidities. The non-survivors had higher baseline neutrophil-to-leukocyte ratio (10.5 vs 8.8), serum ferritin (960 ng/ml vs 611 ng/ml), lactate dehydrogenase (795 IU/L vs 954 IU/L), and D-dimer (5900 μg/ml vs 1485 mg/ml) levels. No drug-related serious adverse effect was noted among the patients.
Conclusion: In a scenario of emerging evidence for the role of TCZ in the management of severe COVID-19, our study provides useful data on its use in the Indian scenario. Deliberate patient selection and timing initiation of TCZ at a crucial stage of the disease may be beneficial in COVID-19 pneumonia with good safety returns.

* *Corresponding author.*
E-mail address: majrkapoor@gmail.com (R. Kapoor).
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Introduction

The rapid emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as pandemic threw the world into a tizzy and overwhelmed the healthcare system across the world due to the unprecedented transmission rate of the virus. In the absence of a specific antiviral drug, repurposing of several drugs were attempted to meet the enormous challenge.[1–3] The proinflammatory cytokine storm resulting from activation of the immune system was reported to cause multiorgan dysfunction and a major contributor to mortality in initial studies.[4] This led to the recommendation of interleukin-6 receptor (IL-6R) antagonist tocilizumab (TCZ) by National Health Commission of China for severely ill patients on an empirical basis and in an initial report, it was observed to provide a survival benefit.[5] Thereafter, several studies reported the survival benefit of TCZ in severe SARS-CoV-2 related illness.[6,7] However, the outcomes of randomized controlled trials (RCT) did not meet the expected survival benefit and enthusiasm gradually waned off.[8,9] Notwithstanding, the recent findings of REMAP-CAP trial showed a definite survival benefit for the COVID patients in intensive care unit (ICU) which led the National Health System (NHS), Britain, to issue a statement approving the use of tocilizumab and sarilumab for COVID-19 pneumonia patients in ICU.[10,11] The findings of REMAP-CAP trial immunomodulator arm may lead to a resurgence in the use of TCZ and its role in treating COVID-19 pneumonia may have a relook.[11] TCZ is a monoclonal antibody against IL-6R and has been used successfully in many autoimmune and inflammatory conditions.[12,13] Apart from being an anti-inflammatory drug, it also has an antifibrotic effect which becomes pertinent theoretically given pulmonary fibrosis is one of the sequelae of COVID-19 pneumonia.[14] Hence, we report our observation on the use of TCZ in the Indian subset of patients.

Materials and methods

This was a retrospective study conducted at a tertiary care center in India between March 2020 and August 2020. All the patients who were given TCZ had confirmed SARS-CoV-2 virus infection, detected by nasal swab polymerase chain reaction. Before the administration of TCZ, patients were risk stratified by their symptoms into mild (symptomatic but no hypoxia or exertional dyspnea), moderate (required supplemental oxygen by nasal canula or high flow nasal canula and had infiltrates on chest radiograph) and severe (required invasive mechanical ventilation).[15]

TCZ was administered only to patients who had at least moderate to severe COVID-19 with laboratory features of inflammation viz raised C-reactive protein (CRP; more than 6 mg/L), raised ferritin (more than 500 ng/ml), raised lactate dehydrogenase (LDH; more than 500 IU/L), raised D-dimer (more than 500 ng/ml) and had not responded to standard of care treatment.

Patients with severe neutropenia (less than 500 cells/cmm) and evidence of coexisting non-COVID-19 infection, and history suggestive of any gastrointestinal bleed were not given TCZ therapy. Two doses of TCZ were given 12 h apart by intravenous route at recommended dose 8 mg/kg body weight (maximum 800 mg).

Standard of care treatment

On admission, all patients were started on the standard of care treatment as per the prevailing institutional/national guidelines. The standard of care treatment has been revised with time, based on the emerging evidence in support of different therapeutic agents. All patient received broad-spectrum antibiotics and low-molecular-weight heparin in therapeutic doses (enoxaparin 1 mg/kg body weight twice daily). In the initial phase, methylprednisolone (2 mg/kg body weight intravenously once daily) was administered as glucocorticoid agent. It was replaced by dexamethasone (10 mg intravenously once daily) as the standard choice of glucocorticoid later. Recovery trial result was published.[16] Antiviral agent Remdesivir (200 mg loading dose followed by 100 mg once daily for additional 4 to 9 days) and convalescent plasma therapy was administered depending upon the disease severity and availability. Doses of drugs were adjusted in presence of renal or hepatic function compromise on case-to-case basis.

Indications for mechanical ventilation included deterioration in sensorium (Glasgow coma scale less than 8), respiratory failure (defined as respiratory rate more than 30 breaths per minute with the use of accessory muscles of respiration). Post-TCZ administration patients were monitored clinically and markers of inflammation were repeated daily to assess the progression of the disease.

Complete blood count parameters were analyzed using the Sysmex XT-2000i hematology analyzer using fluorescence flow cytometry (FFC) technology. The neutrophil-lymphocyte ratio (NLR) was calculated from the differential leukocyte counts values. Serum ferritin was measured by VIDAS® Ferritin by Enzyme Linked Fluorescent Assay technique. The maximum value of serum ferritin detected by the kit was 1200 ng/ml. Biochemical parameters were measured using, Transasia 360 automated analyzer. The upper level of normal value for lactate dehydrogenase (LDH), aspartate transaminase (AST), and alanine transaminase (ALT) were 450 U/L, 35 IU/L and 40 IU/L respectively. D-dimer was measured using VIDAS® D-dimer by Enzyme Linked Fluorescent Assay technique (the normal value being less than 500 μg/ml, FEU). The data of laboratory parameters from the day of admission to day 14 post-TCZ administration were recorded in an Excel sheet and analyzed. Approval of the institutional ethical committee was obtained.

Statistical analysis

Documented records from all patients were perused and data was compiled manually in an Excel sheet. Also, a comparative tabulation of various parameters between the survivors and non-survivors was done. Normally distributed continuous variables were expressed as mean and standard deviation (SD) while data not following normal distribution were expressed as median and minimum (min) and maximum (max) values respectively. Categorical variables were expressed in numbers

and percentage (%). Due to small sample size, no test for statistical significance was done. The computation of various parameters for expression of data and graphs were prepared using the R software.

Results

A total of 21 patients were given TCZ at our center between May 2020 and August 2020. Their demographic profile is presented in Table 1. The individual details on demographic and clinical parameters, treatment and outcome of the patients have been presented in Table 2. Out of 21, 6 (28.5%) patients were females and 15 (71.5%) were male. The median age was 63 years (min 5 years, max 82 years). Six patients (4 male and 2 female) were below 50 years of age and rest 15 patients (11 male, 4 female) were 50 years or older. The median age of the female patients was 64.5 years (minimum 40 years, maximum 82 years), while male patients had a median age of 63 years (minimum 5 years, maximum 79 years). Of the 21 patients only one was from the pediatric age group (less than 12 years). The median BMI of all patients was 23 kg/m^2 (min 18 kg/m^2, max 30 kg/m^2).

Hypertension and type 2 diabetes mellitus were the most common comorbidities present in 8 patients each. Other comorbidities have been presented in Table 1. Two patients had rheumatological comorbidities which included rheumatoid arthritis (RA) and juvenile idiopathic arthritis (JIA). They presented with flare of underlying rheumatological conditions and simultaneously had features of mild COVID-19. Although both these patients had persistent symptoms and gradual rise in markers of inflammation despite standard of therapy for COVID-19, administration of TCZ was prompted by the active rheumatological condition, that is, RA and JIA for which it is one of the standard of care drug. They are included in the study as it enhances our experience of use of TCZ in COVID-19.

There were 13 (62%) patients who recovered (survivors) from COVID-19 and were discharged from the hospital at the time of writing this manuscript and 8 (32%) patients succumbed (non-survivors) to the illness. Comparative demographic profile and laboratory parameters of survivors and non-survivors are presented in Table 1. Due to small sample size, the statistical significance of the difference of parameters between the two groups has not been analyzed. Out of 21, 16 patients had severe disease at the time of TCZ administration and among them, 8 (50%) survived. Three patients had moderate and two had mild disease and all of them survived. Among the non-survivors, two patients died on the 4th day post-TCZ administration, one patient died on day 5, two

Table 1 – Baseline demographic profile and clinical and laboratory parameters of study patients at tocilizumab administration and additional treatment given to them.

	Total (21)	Survivors (13)	Non-survivors (8)
Age in years, median (min, max)	63 (5,82)	68 (5, 82)	53.5 (40, 79)
Patients of ≥50 years of age, n (%)	15 (71)	9 (70)	6 (75)
Male/female (n)	15/6	11/2	4/4
BMI in kg/m^2 median (min, max)	23 (18,30)	24 (18,30)	22 (21, 28)
Number of days of symptoms median (min, max)	8 (3, 15)	6 (3, 14)	12 (9, 15)
Comorbidities in number (%)			
Type 2 diabetes mellitus	8 (38)	3 (23)	5 (63)
Hypertension	8 (38)	4 (31)	4 (50)
Coronary artery disease	5 (23)	1 (8)	4 (50)
Chronic kidney disease	2 (10))	0 (0)	2 (25)
Juvenile idiopathic arthritis	1 (5)	1 (8)	0 (0)
Rheumatoid arthritis	1 (5)	1 (8)	0 (0)
No comorbidities	7 (33)	5 (38)	2 (25)
COVID-19 risk stratification before tocilizumab administration in number (%)			
Severe	16 (76)	8 (62)	8 (100)
Moderate	3 (16)	3 (23)	0 (0)
Mild	2 (10)	2 (16)	0 (0)
Laboratory parameters prior when TCZ was administered			
Hemoglobin in g/dl, median (min, max)	12.2 (7.2,14.7)	11.8 (10.2, 14.7)	9 (7.2, 13)
Total leukocyte count median (min, max)	10,960 (3900,20490)	10,570 (7000, 20,460)	10,330 (3900, 20,490)
NLR median (min, max)	9 (1,30)	8.8 (1, 30)	10.5 (1,30)
Ferritin in ng/ml, median (min, max)	1000 (30,1200)	611 (30, 1200)	960 (787, 1200)
LDH in IU/L, median (min, max)	1026 (325, 2929)	795 (325, 1781)	954 (906, 2929)
D-dimer in μg/ml, median (min, max)	1553 (269, 8600)	1485 (269, 4445)	5900 (1013, 8600)
Additional treatment given to the number of patients			
Methylprednisolone	4	3	1
Dexamethasone	15	8	7
Remdesivir	7	3	4
Convalescent plasma	2	1	1

BMI: body mass index; COVID-19: coronavirus disease 2019; IU: international units Kg: kilogram; LDH: lactate dehydrogenase; m: meter; Min: minimum; Max: maximum, n: number; NLR: neutrophil-lymphocyte ratio.

Table 2 – Individual patient's demographic, clinical parameters, treatment and outcome.

Patient No	Age (yr)	Sex	Comorbidities	Body mass index (kg/m^2)	COVID-19 Class	Days of symptoms prior to TCZ	Standard and additional treatment received[a]	Outcome	Death after days post TCZ
1	69	M	CAD	24	Moderate	6	Methylprednisolone	Recovered	
2	55	F	DM, HTN, CAD	21	Severe	13	Methylprednisolone	Dead	15
3	63	M	HTN, CAD	26	Severe	7	Methylprednisolone	Recovered	
4	80	F	None	27	Moderate	9		Recovered	
5	52	M	None	22	Severe	12	Dexamethasone	Dead	9
6	70	M	CAD	21	Severe	5	Dexamethasone	Recovered	
7	79	M	CAD	20	Severe	15	Dexamethasone	Dead	4
8	5	M	JIA	18	Mild	4	Methylprednisolone	Recovered	
9	41	M	RA	23	Mild	3		Recovered	
10	50	M	None	21	Severe	11	Dexamethasone, Remdesivir, convalescent plasma	Dead	18
11	64	M	None	30	Moderate	7	Dexamethasone	Recovered	
12	69	M	None	26	Severe	8	Dexamethasone	Recovered	
13	31	M	None	19	Severe	6	Dexamethasone	Recovered	
14	73	M	DM,HTN	27	Severe	5	Dexamethasone	Recovered	
15	63	M	DM, HTN, CKD	28	Severe	9	Dexamethasone	Dead	10
16	40	F	DM	21	Severe	10	Dexamethasone, Remdesivir	Dead	9
17	47	F	DM, HTN	24	Severe	12	Dexamethasone, Remdesivir	Dead	4
18	68	M	DM,HTN	22	Severe	14	Dexamethasone, Remdesivir, convalescent plasma	Recovered	
19	74	F	DM,HTN,CKD	26	Severe	15	Dexamethasone, Remdesivir	Dead	5
20	45	M	None	23	Severe	8	Dexamethasone	Recovered	
21	82	F	DM,HTN	29	Severe	5	Dexamethasone, Remdesivir	Recovered	

CAD: coronary artery disease; CKD: Chronic kidney disease; DM: diabetes mellitus; HTN: hypertension; JIA: juvenile idiopathic arthritis; RA: rheumatoid arthritis; TCZ: tocilizumab.

[a] All patients were given antibiotics and low-molecular-weight heparin as standard of care in addition to the drugs mentioned in the column.

patients died on day 9, one patient died on day 10. Thus, at 14 days post TCZ, only 2 out of 8 were surviving and they succumbed to the illness on day 15 and day 18.

The follow-up data of different laboratory parameters monitored in the patients have been compared in the survivors and non-survivors using a line diagram. Fig. 1 shows the median values of hematological parameters at follow up points. The non-survivors had lower baseline (at the time of TCZ administration) median hemoglobin (9 g/dl) as compared to the survivors (11.8 g/dl). The median leukocyte count at baseline was comparable in the survivors (10,570/μl) and non-survivors (10,330/μl). However, following TCZ administration, in the non-survivor group, the median TLC increased and continued to remain higher while the survivors experienced a decline in the median TLC. The median platelet count was normal in both the groups at baseline; however, the non-survivors experienced a gradual decline in platelet count (Fig. 1). The median serum AST and ALT remained identical in both the groups (Fig. 2). However, one patient had experienced an increase in AST and ALT more than 5 times the upper level of normal. This individual had transient hypotension before he developed a rise in transaminases. The median values of serum ferritin, LDH, NLR, and D-dimer in the survivors and non-survivors are represented in Fig. 3. The median D-dimer at baseline was comparable in both groups; however, there was a persistent rise in the non-survivor group (Fig. 2a). Serum ferritin level was also comparable in both the groups before the TCZ administration. However, post-TCZ administration the serum ferritin reduced remarkably in the survivor group while it remained persistently increased in the non-survivors (Fig. 2b). Serum LDH and NLR were also comparable in both the groups at TCZ administration; however, the non-survivors had experienced a persistent rise in NLR and LDH in the course of illness post-TCZ administration.

Discussion

In our study 8 (32%), patients died and all of them were on mechanical ventilation when TCZ was administered. As compared to the survivors, the non-survivors had a longer duration of symptoms at the time of TCZ administration (6 days in survivors vs 12 days in non-survivors). Besides, non-survivors had more medical comorbidities and all of them had severe COVID-19 (8 out of 8 vs 8 of 13). Pre-existing co-morbidities like diabetes

Fig. 1 – The median of hematological parameters of the study patients at various days during follow-up; (a) hemoglobin in g/dl, (b) platelets in thousands per μl, (c) white blood cell count in numbers per μl.

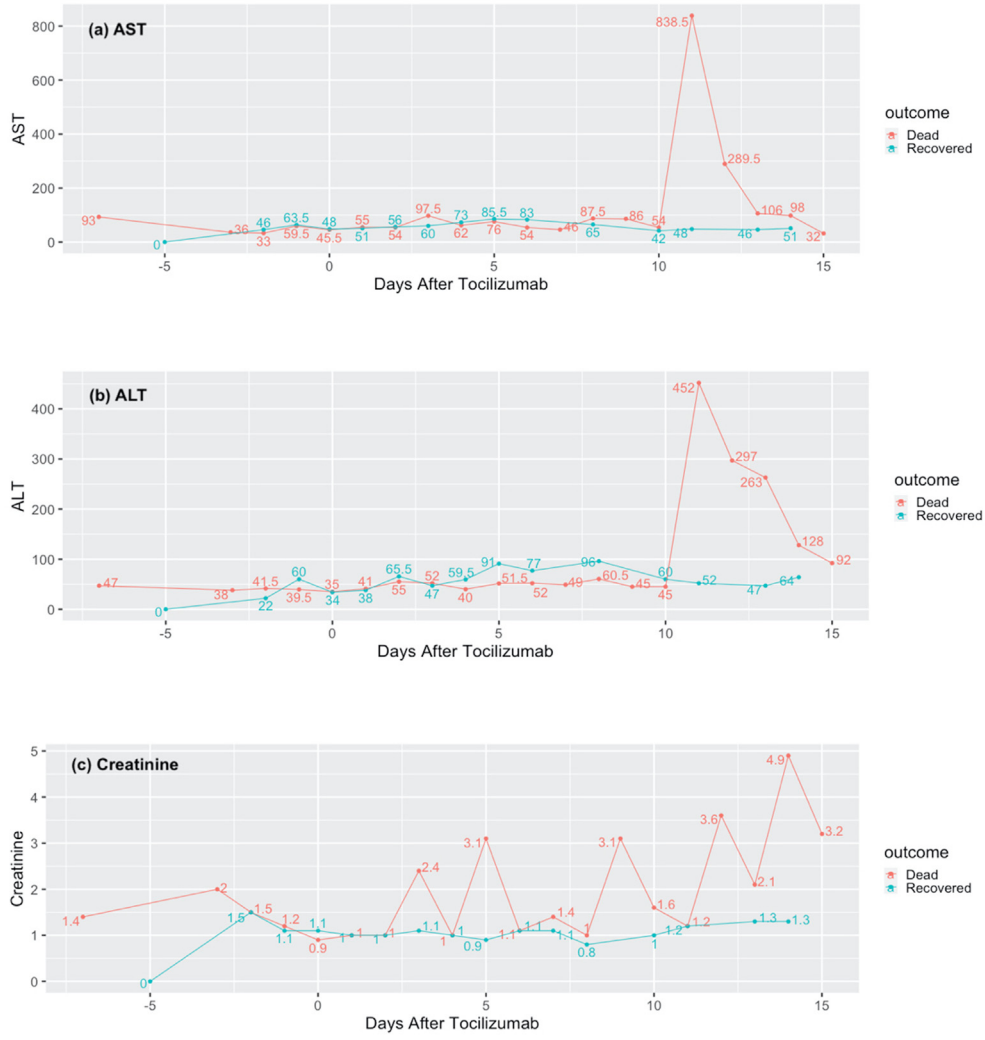

Fig. 2 – The median of biochemical parameters the study patients at various days during follow-up; (a) aspartate transaminase in IU/L, (b) alanine transaminase in IU/L, (c) creatinine in mg/dl.

mellitus, chronic kidney disease, hypertension and longer duration of the disease have already been reported as predictors of increased mortality.[17] Increased age is a risk factor for mortality in COVID-19; however, in our study, the non-survivors relatively had lower age (median age 53.5 years than the survivors (median age 68 years). Apparently, the presence of comorbidities and severity of disease had an offsetting effect on the putative advantage of lower age profile among the non-survivors. Leukocytosis, raised creatinine, and anemia have been earlier reported to be associated with increased mortality.[18,19] Non-survivors in our study too had relatively lower hemoglobin, leukocytosis and raised creatinine.

COVID-19 pneumonia and timing of TCZ use

None of the five patients who had moderate or mild disease progressed to require invasive ventilation in our study while eight (32%) patients with severe disease survived in our study. Thus, it appears that high mortality in our study is due to the higher proportion of patients with severe disease. Although TCZ appears to have benefited the patients with severe disease also, it appears that time of administration of TCZ is crucial and the maximal gain can be achieved by administering it in moderate COVID-19–related pneumonia before it progresses to a severe disease requiring invasive ventilation. This observation is supported by the study in which TCZ was used at the early stage of respiratory failure. In this study, only 7.7% (7 out of 90) of the patients who received TCZ died as compared to 50% (34 out of 68) of patients who did not receive TCZ.[20] In the study by Xu X et al, 17 out of 21 patients treated with TCZ were not on mechanical ventilation at the time of TCZ administration and all of them were discharged from the hospital after recovery.[6] In another study, duration of symptoms at the time of TCZ administration was significantly associated with the outcome of COVID-19 and administration of TCZ within 12 days of onset of symptoms was associated independently with 28 days survival.[21] Thus, it appears that with careful patient selection and timing the administration of TCZ at an early stage of the disease and early during the respiratory failure may improve the outcome of COVID-19.

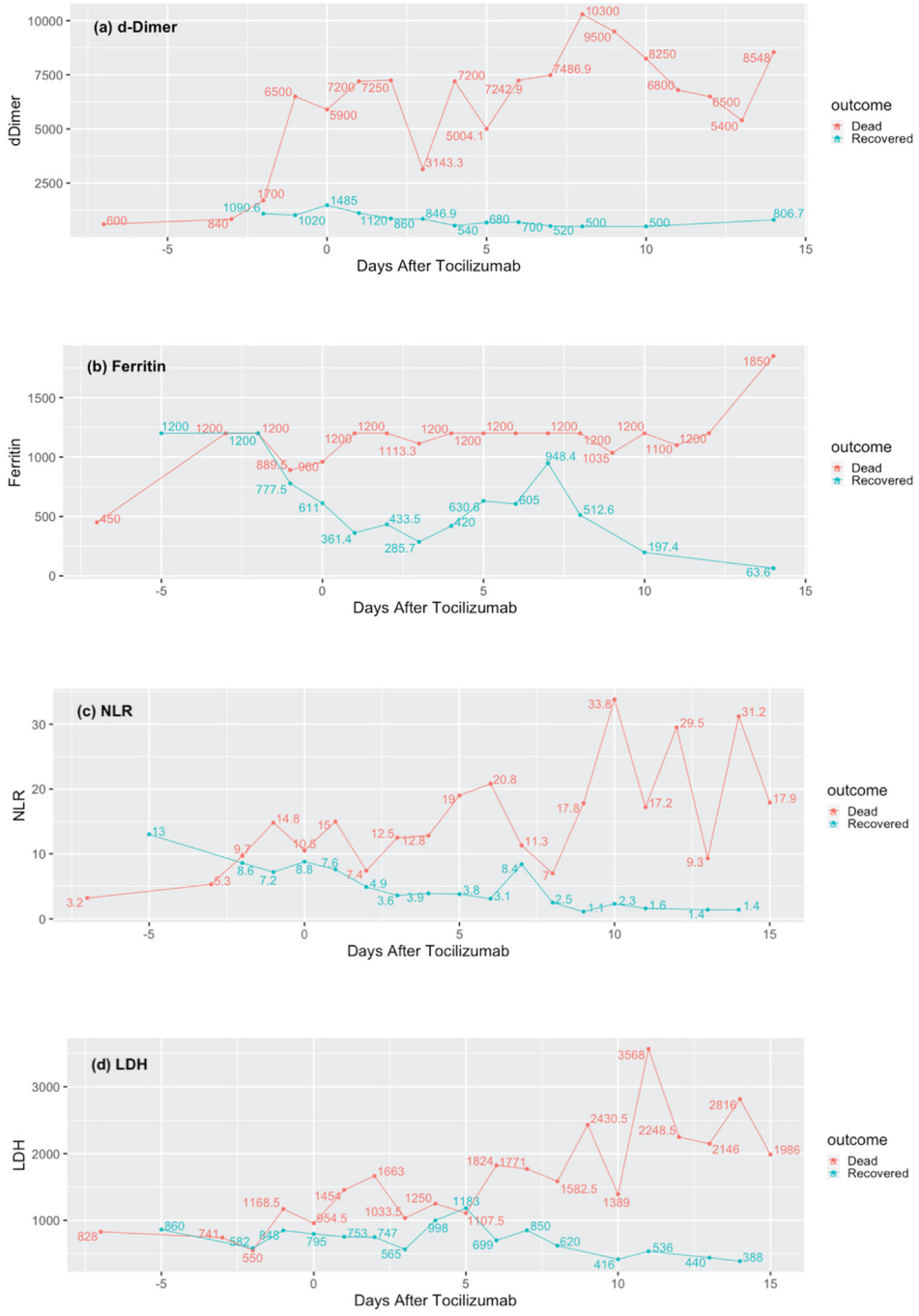

Fig. 3 – The median of markers of inflammation at various days of follow-up; (a) D-dimer in μg/L, (b) ferritin in ng/ml, (c) neutrophil-lymphocyte ratio (NLR), (d) lactate dehydrogenase (LDH) in IU/L.

Emerging evidence for TCZ in COVID-19 pneumonia

Although many observational studies reported the benefit of TCZ in COVID-19, the first phase-III RCT (COVACTA) failed to reach its primary endpoint and there was no difference in clinical status of the patients in TCZ and placebo arm at four weeks of treatment assessed by 7-category ordinal scale.[8] Although, the ventilation-free days were longer in the TCZ arm, the percentage of patients who died at four weeks was similar in both arms.[8] On the contrary, another recently reported phase III RCT, the EMPACTA trial, met its primary endpoint and patients receiving TCZ in COVID-19 pneumonia had 44% fewer chances of death or requirement of mechanical ventilation (p-value 0.0348; hazard ratio [95% confidence interval] 0.56 [0.32, 0.97]).[22] In the REMAP-CAP trial, mortality in the placebo group was 35.8% as compared to 27% in the treatment group, which led to an overall 24% reduction in risk of death. In addition to survival benefit, time to recovery benefit has also been reported with a reduction in more than a week time spent in the ICU.[11] In a retrospective study from India, the authors have reported reduced incidence

of death and need for mechanical ventilation in moderate to severe COVID-19 pneumonia patients with inflammatory syndrome who did not respond to glucocorticoids.[23] Thus, the evidence in respect to the efficacy of TCZ in COVID-19 treatment is still emerging and it may be an important part of the therapeutics in the management of COVID-19.

Serum ferritin, D-dimer, LDH, and NLR are the surrogate markers of the hyperinflammatory syndrome associated with COVID-19 and these factors have been reported to be associated with COVID-19 severity and mortality.[24,25] In our study, also these markers were remarkably higher in non-survivors during illness. The additional treatment given to the patients including dexamethasone, remdesivir or convalescent plasma were similar among both groups of patients. In all the non-survivors in our study NLR, ferritin, D-dimer and LDH did not improve after TCZ administration. In comparison, the survivor patients experienced a gradual decline in these biomarkers. However, it cannot be concluded whether a declining trend in these biomarkers may indicate a favorable response to the treatment.

Safety of TCZ

A rise in AST and ALT is a known complication of TCZ treatment.[26] In one of our patient's, AST and ALT increased, albeit, on the day 10 following TCZ injection and was likely due to ischemic hepatic injury secondary to hypotension. Other study patients did not show any remarkable rise in serum AST or ALT following TCZ administration and the median level of AST and ALT did not reach the two times the upper level of normal. There were no other safety issues noted. The COVACTA trial also did not report any new safety issue for use of TCZ in COVID-19.[8]

Our study is one of the first few in India to report the use of TCZ in COVID-19 and it largely corroborates with the findings of other studies.[23,27] Although this study is limited by small sample size and lack of a control arm, it provides a set of facts and data which can be useful for the clinicians involved in COVID-19 management in India. Initial results from REMAP-CAP trial indicate that use of TCZ in COVID-19 cannot be entirely written off and once the results are published, use of TCZ may see a resurgence, thereby rendering our study more relevant for Indian scenario.[11]

Conclusion

In a situation where evidence for the role of TCZ in the management of severe COVID-19 is still emerging, our study provides useful data on its use in the Indian scenario. Deliberate patient selection and timing of TCZ at a crucial stage of the disease may be beneficial in COVID-19 pneumonia with considerable safety.

Disclosure of competing interest

The authors have none to declare.

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