Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Real World Long-term Assessment of The Efficacy of Tocilizumab in Patients with COVID-19: Results From A Large De-identified Multicenter Electronic Health Record Dataset in the United States

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ABSTRACT

Background: Studies have shown conflicting results on the efficacy of tocilizumab (TCZ) for patients with COVID-19, with many confounders of clinical status and limited duration of the observation. Here, we evaluate the real-world long-term efficacy of TCZ in COVID-19 patients.

Methods: We conducted a retrospective study of hospitalized adult patients with COVID-19 using a large US-based multicenter COVID-19 database (Cerner Real-World Data; updated in September, 2020). The TCZ group was defined as patients who received at least one dose of the drug. Matching weight (MW) and a propensity score weighting method were used to balance confounding factors.

Results: A total of 20,399 patients were identified. 1,510 and 18,899 were in the TCZ and control groups, respectively. After MW adjustment, no statistically significant differences in all-cause mortality were found for the TCZ vs. control group (Hazard Ratio [HR]:0.76, p=0.06). Survival curves suggested a better trend in short-term observation, driven from a subgroup of patients requiring oxygen masks, BIPAP or CPAP.

Conclusion: We observed a temporal (early) benefit of TCZ, especially in patients on non-invasive high-flow supplemental oxygen. However, the benefit effects faded with longer observation. The long-term benefits and risks of TCZ should be carefully evaluated with follow-up studies.

Background

Severe acute respiratory syndrome caused by SARS-CoV-2 (COVID-19) was originally described in Wuhan, Hubei province. SARS-CoV-2 has spread worldwide, causing more than 600,000 deaths in the (United States) U.S. as of Aug 2021 (Johns Hopkins COVID-19 Dashboard). Severe COVID-19 is characterized by pneumonia, which may progress to acute respiratory distress syndrome (ARDS) and respiratory failure. Severe cases of COVID-19 leading to alveolar damage, respiratory failure, and ARDS seem to be associated with a pro-inflammatory state (cytokine storm), likely mediated by interleukin 6 (IL-6), interferon-gamma, and granulocyte-macrophage colony stimulator among others (Xu et al., 2020; Ye et al., 2020). Many patients require mechanical ventilation and, in some cases, the use of extracorporeal membrane oxygenation (ECMO) (Jacobs et al., 2020).

Treatment strategies for COVID-19 include antiviral medications (i.e., remdesivir) and immunomodulatory therapies (i.e., corticos-

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teroids and anti-IL-6 receptor inhibitors). (Sanders et al., 2020). Remdesivir has shown some benefits, including a shorter time to recovery in the phase 3 clinical trial (Beigel et al., 2020), although its effect on mortality is questionable. Indeed, the World Health Organization (WHO) did not endorse remdesivir use in hospitalized patients based on the absence of benefits from the WHO SOLIDARITY trial (WHO Solidarity Trial Consortium et al., 2020). A large randomized controlled trial from the United Kingdom (UK) indicated that dexamethasone significantly decreased mortality in patients with COVID-19. The effects were most pronounced in patients on mechanical ventilation (RECOVERY Collaborative Group et al., 2020). Tocilizumab (TCZ), a recombinant anti-IL-6 receptor monoclonal antibody, emerged as a potential therapeutic option for patients with severe COVID-19 due to its counteracting immunomodulatory effects on the cytokine storm (Xu et al., 2020; Ye et al., 2020). Recent clinical data from the REMAP-CAP trial indicated that TCZ offered a mortality benefit in patients with COVID-19 within 24 hours of organ support in an intensive care unit (ICU). This result led the U.K. National Health Service (NHS) to support the off-label use of interleukin-6 antagonists (UK NHS Website). More recently, the RECOVERY trial that included more than 4,000 patients revealed a significant mortality benefit for the use of tocilizumab (Abani et al., 2021). Nonetheless, some other studies did not provide positive results on the administration of TCZ for COVID-19 (Rosas et al., 2021; Salvarani et al., 2020; Stone et al., 2020). In the setting of possible conflicting results, we sought to assess the real-world use of TCZ with a longer observation period in patients with COVID-19 stratified by specific subgroups using a large de-identified multicenter electronic health record (EHR) database in the U.S.

Methods

This study used the Cerner Real World Data (CRWD) COVID Database, a large de-identified EHR database. The database consists of 490,373 patients from 87 hospitals with longitudinal data, including demographics, diagnostic (ICD10) codes, vital signs, medications, and laboratory data. Our study used a version of the dataset that was updated in September 2020. The duration of data retrieval was from December 2019 until September 2020. Our study included patients 18 years or older who were hospitalized with a positive SARS-CoV-2 PCR test during the encounter or within two weeks prior to the index of admission. The TCZ cases were defined as patients who received at least one dose of TCZ within five days of admission. The patients who did not receive TCZ during hospitalization were treated as controls. The baseline characteristics of the TCZ group were obtained before the initiation of TCZ. In the control group, baseline characteristics were retrieved within five days after admission. The five-day baseline period was determined based on the 75% interquartile duration of hospitalization before initiation of TCZ in the overall population who received the drug in the dataset. Patients who died within the baseline period were excluded for mortality outcome, and those intubated during the baseline period were excluded for the intubation outcome analysis. Corticosteroid use was defined as the administration of dexamethasone 6 mg per day or more (or the equivalent dosage in other steroid formulations) based on a previous study (RECOVERY Collaborative Group et al., 2020). We also collected information regarding the use of medications frequently used for the management of patients with COVID-19, such as hydroxychloroquine, azithromycin, remdesivir, convalescent plasma, and therapeutic anticoagulation. Therapeutic anticoagulation was defined as intravenous formulations of heparin or enoxaparin at doses greater than 40 mg/day. Comorbidities were obtained based on ICD-10 codes. The median PaO2/FiO2 ratio during the baseline period was calculated using oxygen saturation and the required mode of oxygen delivery, based on methods developed by Brown et al. (Supplementary material).(Brown et al., 2017). Additional laboratory data extracted included those related to the severity of the disease and potential risk factors for the progression of the disease, such as inflammatory markers. The duration of observation was analyzed based on the day of discharge or the most recent date of observation during the hospitalization if the patients were not discharged from the hospital. For subgroup analysis, both groups were further divided into two comparative groups, as follows: ***i***) patients who were on and off mechanical ventilation and ***ii***) patients who were on corticosteroids or those who did not receive corticosteroids during the baseline period. The outcomes of our study were all-cause hospital mortality and endotracheal intubation after initiation of TCZ. All-cause hospital mortality was defined as death or discharge to hospice, with the date of discharge of hospice patients being defined as the date of death. Microbiology data were not available in this database.

A propensity score analysis was performed to compare outcome variables between the TCZ and control groups using Matching Weight (MW), a propensity score weighting method,(Li and Greene, 2013) to achieve balance in baseline covariates between the TCZ and control groups and remove confounding factors from these covariates. The propensity scores were calculated by fitting a logistic regression to the treatment group indicator with baseline covariates. The outcome variables were compared between the treatment groups after weighting. Standardized mean differences (SMD) were used to evaluate balance before and after weighting (Supplementary material). Since there were missing data in baseline covariates , we used multiple imputation (mice package version 3.12 in R) for missing values in covariates and produced five imputed datasets. The aforementioned propensity score weighting procedure was performed on each dataset and subgroup analysis (Table S1-A-G), and the final estimators of the treatment effects on the outcomes were formed using the multiple imputation formula. Statistical analysis was conducted with R ver 3.6.3 (The R Foundation) and Python ver.3.7.6 (Python Software Foundation).

Results

A total of 490,373 patients were identified from the database. After applying the inclusion-exclusion criteria, 20,409 patients were included in the analyses (Figure 1). 2,775 patients received at least one dose of TCZ during the index of hospitalization. 2,171, 496, and 108 patients received one, two, or $\geq$ 3 doses of TCZ, during hospitalization, respectively. After the exclusion of patients who received TCZ after five days of hospitalization, 1,510 patients were included in the case group. The remaining 32,183 patients did not receive TCZ. 13,284 patients in the control group did not have any measurements of inflammatory markers and other baseline labs, such as serum interleukin-6 level, C-reactive protein, sedimentation rate, and lactate dehydrogenase (LDH) within the range of baseline periods. Those patients were excluded from the control group to optimize multiple imputations. Thus, a total of 18,899 patients were included in the control group.

The baseline characteristics before multiple imputations are summarized in Table 1. In the unadjusted cohort, the TCZ group differed in variables except for asthma, human immunodeficiency virus (HIV), and solid organ transplant (SOT) (Standardized mean differences [SMD] of those variables were less than 10%). The TCZ group had 439 patients (39.5%) on mechanical ventilation during the baseline periods, whereas the control group only had 3,173 (24.6%) patients. Of note, corticosteroids were used during the baseline periods in 547 patients (36.2%) and 9,160 patients (48.5%) in the TCZ and control groups, respectively. After adjusting with the MW method, both groups were balanced based on SMD ($<$10% is considered optimal balance) (Table 1). The final cohort had a

Table 1
Descriptive Analysis of Cohort Data Before and After Adjustment with Propensity Score

	Before Multiple Imputation &MW Adjustment[a]			After MW Adjustment[b]		
Characteristic	Tocilizumab N=1,510	Control N=18,899	SMD[c]	Tocilizumab	Control	SMD[c]
Age (years old)Median (IQR)	62(51-71)	64(52-75)	15.9	63(52-71)	62(51-73)	1.0
Gender, Male (%)	983 (65.1%)	10196 (53.9%)	22.9	63.1%	63.4%	0.3
Ethnicity/Race, N (%)						
Hispanic or Latino	623 (41.3%)	7214 (38.2%)	2.4	44.3%	45.2%	3.6
White	391 (25.9%)	5857 (31.0%)	32.9	24.8%	24.6%	1.8
African American	322 (21.3%)	3618 (19.1%)	9.2	19.9%	19.1%	3.0
Asian	61 (4.0%)	416 (2.2%)	30.5	3.6%	3.7%	1.3
Other	113 (7.5%)	1794 (9.5%)	10.9	7.4%	7.4%	0.6
Hospital size(bed size), N(%)						
6-99	17 (1.1%)	95 (0.5%)	6.9	1.2%	1.1%	0.6
100-199	0 (0.0%)	125 (0.7%)	11.5	0%	0%	0.1
200-299	22 (1.5%)	349 (1.8%)	3.1	1.9%	2.0%	0.1
300-499	152 (10.1%)	1175 (6.2%)	14.1	8.0%	7.8%	1.2
500-999	414 (27.4%)	4157(22.0%)	12.6	26.2%	27.0%	1.0
>1000	905 (59.9%)	12998 (68.8%)	18.5	62.8%	62.2%	0.2
Division Census						
New England	62 (4.1%)	280 (1.5%)	16.0	2.7%	2.7%	1.0
Middle Atlantic	497 (32.9%)	3338 (17.7%)	35.6	31.8%	31.8%	0.7
East North Central	72 (4.8%)	1141 (6.0%)	5.6	4.2%	3.9%	1.4
West North Central	15 (1.0%)	725 (3.8%)	18.6	1.6%	1.7%	2.0
South Atlantic	519 (34.4%)	4911 (26.0%)	18.3	34.4%	33.9%	3.2
East South Central	36 (2.4%)	356 (1.9%)	3.5	3.0%	3.1%	1.3
West South Central	21 (1.4%)	1351 (7.1%)	28.8	2.2%	2.0%	0.7
Mountain	5 (0.3%)	4432 (23.5%)	76.5	0.5%	0.5%	0.5
Pacific	283 (18.7%)	2365 (12.5%)	17.2	19.6%	20.4%	3.7
Comorbidities, N (%)						
Dementia	31 (2.1%)	1609 (8.5%)	29.2	2.7%	2.6%	0.3
CVD	77 (5.1%)	1706 (9.0%)	15.4	5.8%	6.0	0.7
CAD	125 (8.3%)	2795 (14.8%)	20.5	9.5%	9.5%	0.7
CHF	132 (8.7%)	2789 (14.8%)	18.8	10.1%	10.3%	1.5
Asthma	91 (6.0%)	1587 (8.4%)	9.2	6.6%	6.7%	1.4
COPD	174 (11.5%)	3397 (18.0%)	18.3	13.3%	13.6%	2.1
HTN	476 (31.5%)	9888 (52.3%)	43.1	36.4%	36.4%	0.9
DM	509 (33.7%)	8109 (42.9%)	19.0	36.7%	37.1%	1.3
CKD	152 (10.1%)	3343 (17.7%)	22.2	11.7%	11.8%	0.5
HD	52 (3.4%)	1075 (5.7%)	10.8	3.7%	3.6%	0.2
Cirrhosis	8 (0.5%)	407 (2.2%)	14.1	0.7%	0.8%	1.6
Cancer	29 (1.9%)	1100 (5.8%)	20.3	2.4%	2.3%	0.3
HIV	2 (0.1%)	121 (0.6%)	8.2	0.1%	0.1%	0.01
SOT	9 (0.6%)	211 (1.1%)	5.7	0.7%	0.7%	0.6
BMI, Median(IQR)	31.0(26.9-36.1)	31.8(26.6-43.0)	36.7	31.2(27.0-36.8)	30.9(26.9-37.1)	1.5
PaO2/FiO2 RatioMedian, (IQR)	123.5(78.9-184.4)	319.1(167.0-385.7)	127.7	151.5(78.7-250.0)	109.3(76.0-290.5)	5.5
Oxygen Delivery Mode						
Intubation at baseline	439 (39.5%)	3173 (24.6%)	32.4	43.5%	44.7%	3.0
BIPAP/CPAP	117 (10.5%)	1116 (8.7%)	6.4	15.2%	15.1%	1.8
Oxygen Mask	205 (18.5%)	1569 (12.2%)	17.5	17.9%	17.5%	0.6
Nasal Cannula	336 (30.2%)	6869 (53.2%)	48.0	25.0%	24.2%	5.1
Room Air	9 (0.8%)	137 (1.1%)	2.6	3.8%	3.7%	0.5
Vasopressors [c]	75 (5.0%)	138 (0.7%)	25.7	4.4%	4.5%	0.2
Laboratory, Median (IQR)						
Neutrophil counts (k/uL)	11.7(6.2-80.5)	9.0(5.1-67.5)	6.5	12.9(6.7-81.8)	12.6(6.7-80.5)	1.7
Lymphocyte counts (k/uL)	2.0(0.8-9.2)	1.9(0.8-11.0)	5.6	1.7(0.7-8.6)	1.5(0.7-8.8)	1.2
Hemoglobin (g/dL)	12.7(11.4-13.9)	12.1(10.5-13.5)	30.1	12.7(11.4-13.9)	12.7(11.2-14.1)	1.2
Protein (g/dL)	6.7(6.2-7.3)	6.5 (6.0-7.1)	18.5	6.7(6.1-7.2)	6.6(6.1-7.2)	2.4
Total bilirubin (mg/dL)	0.6(0.4-0.8)	0.5 (0.3-0.7)	8.5	0.6(0.4-0.8)	0.6(0.4-0.8)	0.9
Albumin (g/dL)	2.9(2.5-3.2)	2.9 (2.5-3.3)	9.9	2.8(2.4-3.2)	2.8(2.4-3.2)	4.1
ALT (U/L)	37.0(24.0-61.0)	31.0(19.0-54.0)	3.9	37.0(24.0-60.0)	37.0(23.0-61.0)	0.9
AST (U/L)	48.0(33.0-71.0)	37.0(25.0-57.0)	8.1	47.0(32.0-69.0)	47.0(32.0-70.0)	0.7
C-reactive protein (mg/L)	56.5(18.0-187.4)	41.7(13.5-138.3)	20.9	37.0(15.6-181.9)	50.5(16.6-160.0)	0.5
LDH (IU/L)	476.0(349.0-655.0)	403.0(295.0-572.8)	20.2	462.0(337.0-648.0)	478.0(343.0-669.0)	3.1
Ferritin (ng/mL)	968.4(534.4-1716)	657.0(313.7-1312)	7.9	943.3(515.6-1667)	937.0(486.0-1744)	0.9
D-dimer (ng/mL)	1.42(0.77-3.37)	1.39(0.77-3.15)	27.5	1.56(0.81-4.88)	1.80(0.91-4.77)	1.9
Medication, N (%)						
Remdesivir	376 (24.9%)	5604 (29.7%)	10.7	28.4%	28.5%	3.7
Azithromycin	943 (62.5%)	10403 (55%)	15.1	61.7%	61.6%	1.0
Corticosteroids	547 (36.2%)	9160 (48.5%)	25.0	41.6%	41.5%	2.3
Hydroxychloroquine	520 (34.4%)	3211 (17.0%)	40.7	30.6%	30.6%	1.9
Convalescent plasma	21 (1.4%)	423 (2.2%)	6.4	1.97%	1.99%	1.2
Therapeutic Anticoagulation	156 (10.3%)	1987 (10.5%)	0.6	12.0%	12.3%	1.5

[a] Some variables include missing values and affect the denominators.
[b] Continuous variables after adjustment were shown in interquartile range and categorical variables were in proportion.
[c] SMD less than 10% is considered as well balanced between the groups.
[d] Vasopressors include norepinephrine, vasopressin, phenylephrine, and dopamine.MW, Matching Weight, SMD, Standardized Mean Difference, CVD, Cerebral vascular diseases CAD, Coronary artery disease, COPD, Chronic obstructive pulmonary disease, HTN, Hypertension, D.M., Diabetes mellitus, SOT, Solid organ transplant, CKD, Chronic kidney disease, HIV, Human Immunodeficiency virus, CHF, Congestive Heart Failure, CRP, BMI, Body mass index, C-reactive protein, LDH, Lactate dehydrogenase

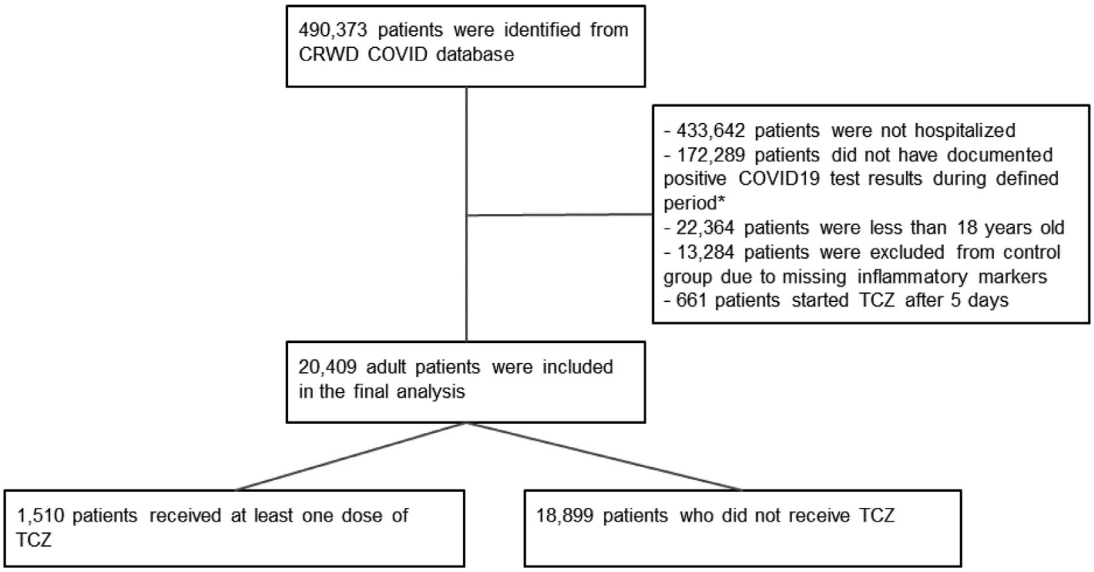

Figure 1. Study Cohort. Some patients met several exclusion criteria. *The defined period was during the index encounter or within 2 weeks before the index hospitalization.

higher proportion of men (63.1 % and 63.4 %, TCZ and control groups, respectively), hypertension (HTN) (36.4 % and 36.4 %), diabetes mellitus (DM) (36.7 % and 37.1 %), and mechanical ventilator use at baseline (43.5 % and 44.7 %). Azithromycin (61.7 % and 61.6 %), corticosteroids (41.6 % and 41.5%), and hydroxychloroquine (30.6% and 30.6 %) were frequently used medications for COVID-19 in the cohort, followed by remdesivir (28.4 % and 28.5%). Due to the log transformation of continuous variables before imputation, only median and interquartile range (IQR) were reported for those variables. The majority of patients were 50 years or older (median 63 [IQR: 52 – 71] and 62 [51 – 73], TCZ and control group, respectively), and had elevated inflammatory markers, such as CRP (median: 37.0 mg/L [IQR: 15.6 – 181.9] and 50.5 mg/L [16.6 – 160.0]), elevated LDH (median 462.0 IU/L [IQR: 337 – 648] and 478 IU/L [343 – 669]), and elevated D-dimer (median 1.56 ng/mL [IQR: 0.81 – 4.88] and 1.80 ng/mL [0.91 – 4.77]).

Table 2 summarizes the outcome analysis in the overall population and subgroup analyses. Before the MW adjustment, the TCZ group had significantly higher mortality (34% vs. 23%, p-value<0.01) and rate of intubation (38.1% vs. 11.6%, p-value<0.01) compared to the control group. After MW adjustment with propensity score methods, TCZ use was not found to be significantly associated with decreased mortality (HR= 0.76, 95% Confidence Interval [CI] 0.49- 1.01, p-value = 0.06). There were no statistically significant differences in mortality in further subgroups analyses, including in patients without mechanical ventilation (HR= 0.93, CI 0.51-1.70, p=0.82), those with mechanical ventilation (HR=0.78, CI 0.50-1.18, p=0.25), and those on BIPAP/CPAP or Oxygen Mask (HR=0.71, CI 0.37-1.39, p=0.33). Baseline corticosteroid use also did not alter the findings between the groups with HR of 0.86 (0.86, CI 0.49-1.5, p= 0.62) and 0.77 (CI 0.07-1.47, p=0.47) for those not receiving corticosteroids and patients on corticosteroids, respectively. TCZ did not change the HR of the outcome (HR=0.90, CI = 0.60-1.36, p = 0.63, and HR = 0.80, CI= 0.26-2.46, p = 0.70) in patients older than 65 years and those with CKD, respectively. Survival curves are shown in Figure 2. In the overall population, the tocilizumab group trended to improved outcomes up to around day 50, however, did not identify as statistical significance. (Figure 2-A). A similar positive trend was observed in the patients with high oxygen supplements, such as BIPAP, CPAP, or oxygen masks (Figure 2-B), but was not observed in other subgroups. Finally, the intubation rate after initiation of TCZ was not different between the groups (HR= 1.77, CI 0.84 – 3.37, p = 0.13).

Discussion

We sought to evaluate the real-world and long-term efficacy of TCZ, taking advantage of the availability of a large sample of data (>20,000 patients) in order to assess the possible benefit of this drug in patients in different stages of COVID-19. Our study revealed that patients who received at least one dose of TCZ did not have improved mortality nor decreased incidence of intubation during their hospitalization after adjustment of baseline characteristics with the MW and propensity score methods. However, survival curves revealed a better trend in short-term observation, which seems mainly driven in the subgroup of patients who required a high amount of non-invasive oxygen supplementation. However, these trends became not significant after long-term observation.

Earlier published clinical trials that used TCZ in COVID-19 patients failed to identify mortality benefits. The Phase III COVACTA trial enrolled hypoxic COVID-19 patients with and without mechanical ventilation. 438 and 144 patients were randomized to TCZ and control group, respectively (Rosas et al., 2021). No mortality benefits were found at day 28 (TCZ group = 19.7% and placebo = 19.4%, p=0.94). The phase III EMPACTA study showed that patients in the TCZ arm (including hypoxic COVID-19 patients without mechanical ventilation) did not exhibit statistically significant differences in mortality (TCZ = 10.4%; placebo = 8.6%, p-value = 0.5146) compared to controls (Salama et al., 2021). In this trial, 55.4% of patients in the TCZ group and 67.2% of those in the placebo group received concomitant dexamethasone. Moreover, two subsequent published clinical trials failed to show the mortality benefits (Salvarani et al., 2020; Stone et al., 2020). The first of such studies (Stone et al., 2020) only included patients without mechanical ventilation, and patients were given dexamethasone. The second study (Salvarani et al., 2020) excluded patients who started corticosteroids for COVID-19 during the enrollment period. However, the limitation of this study was the small number of enrolled patients (N= 60) in the TCZ group. In contrast, the results released from a recent clinical trial assessing TCZ in COVID-19 (REMAP-CAP) showed that TCZ improved mortality in patients requiring organ support within 24 hours in the ICU (REMAP-CAP In-

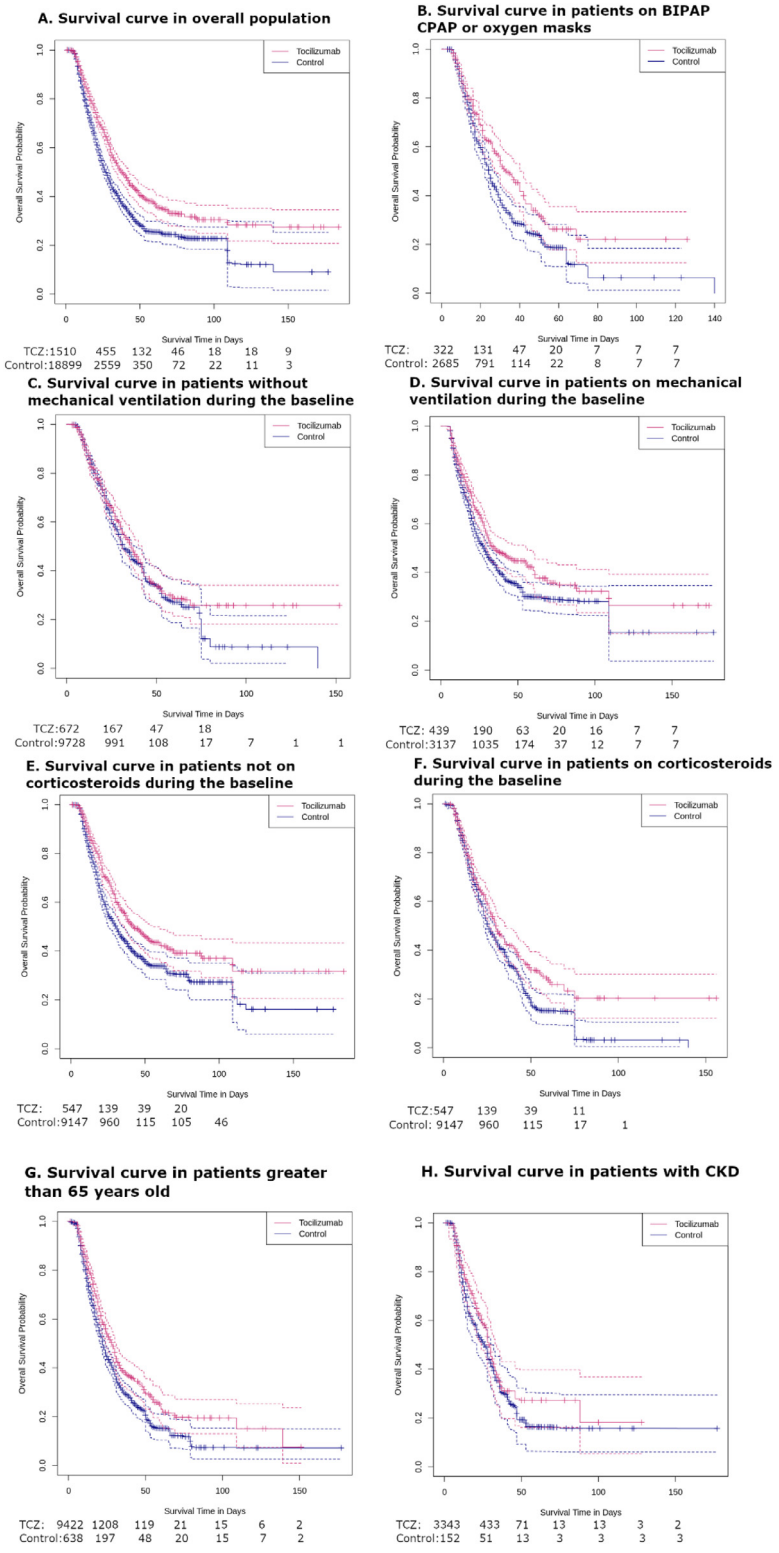

Figure 2. Survival Curves in Overall Cohort and Subgroups. Cumulative survival probability curves were shown in the overall populations (Panel A), in patients with BIAP/CPAP or oxygen mask (Panel B), those without mechanical ventilation (Panel C), those on mechanical ventilation (Panel D), those on corticosteroid use during the baseline (Panel E), in those with corticosteroids use (Panel F), in those greater than 65 years old (Panel G), and with CKD (Panel H). This graph was drawn based on one of the five imputed data. Hazard ratios and p-values were calculated with pooled five imputed data. TCZ, Tocilizumab, N, Number, CKD, Chronic Kidney Diseases

Table 2
Main Results and the Subgroup Analyses After Multiple Imputations

	Before Adjustment			After MV Adjustment		
	TocilizumabN=1510	ControlN=18,899	HR(95% CI)p-value	Tocilizumab	Control	HR(95% CI)p-value
Hospital Mortality	509 (34 %)	4371 (23 %)	0.81(0.74 - 0.89)p < 0.01	34.7 %	38.0 %	0.76(0.49 –1.01),p=0.06
Subgroup Analysis						
Patients Without Mechanical Ventilation during the Baseline Period						
	TocilizumabN=672	**ControlN=9728**	**HR(95% CI)p-value**	**Tocilizumab**	**Control**	**HR(95% CI)p-value**
Hospital Mortality	209/672(31.1%)	1978/9728(20.3%)	0.78(0.68 - 0.91)P<0.01	32.5 %	29.2 %	0.93(0.51 – 1.70),p=0.82
Intubation	256/672*(38.1 %)	1127/9728*(11.6 %)	1.89 (1.57-2.28)P<0.01	25.6 %	18.6 %	1.77(0.84-3.73),p=0.13
Patients With Mechanical Ventilation during the Baseline Period						
	TocilizumabN= 439	**ControlN= 3173**	**HR(95% CI)p-value**	**Tocilizumab**	**Control**	**HR(95% CI)p-value**
Hospital Mortality	204/439(46.4%)	1530/3173(48.2%)	0.78(0.68 - 0.91)p=0.01	46.2%	48.9%	0.78(0.50-1.18),p = 0.25
Patients on BIPAP/CPAP or Oxygen Mask during the Baseline Period						
	TocilizumabN = 322	**ControlN = 2685**	**HR(95% CI)p-value**	**Tocilizumab**	**Control**	**HR(95% CI)p-value**
Hospital Mortality	140/322(43.5%)	1101/2685(41.0%)	0.73(0.61-0.88)P<0.01	44.7%	47.5%	0.71(0.37-1.39)P = 0.33
Intubation	81/237*(34.2%)	622/2506*(24.8%)	1.23(0.97-1.55)P=0.08	51.4%	40.2%	1.01(0.51- 2.28)P = 0.84
Patients Not Receiving Corticosteroids during the Baseline Period						
	TocilizumabN=963	**ControlN=9739**	**HR(95% CI)p-value**	**Tocilizumab**	**Control**	**HR(95% CI)p-value**
Hospital Mortality	313/963(32.5%)	2181/9739(22.4%)	0.84(0.74-0.95)P < 0.01	33.2%	40.0%	0.86(0.49-1.5)p =0.62
Intubation	158/399*(39.6%)	533/4386*(12.2%)	1.699(1.31 - 2.21)P<0.01	40.2%	27.5%	1.53(0.54-4.33)p=0.43
Patients Receiving Corticosteroids during the Baseline Period						
	TocilizumabN=547	**ControlN= 9160**	**HR(95% CI)p-value**	**Tocilizumab**	**Control**	**HR(95% CI)p-value**
Hospital Mortality	196/547(35.8%)	2190/9160(23.9%)	0.82(0.71 - 0.96)P = 0.01	38.3%	37.4%	0.77(0.07-1.47)p=0.47
Intubation	98/273*(35.9%)	594/5342*(11.1%)	1.61(1.24-2.09)P<0.01	36.2%	27.2%	1.17(0.45 - 3.0)P = 0.75
Patients Age Greater than 65 years old						
	TocilizumabN=638	**ControlN= 9422**	**HR(95% CI)p-value**	**Tocilizumab**	**Control**	**HR(95% CI)p-value**
Hospital Mortality	301/638(47.2%)	3079/9422(32.7%)	0.83(0.79 - 0.87)P<0.01	49.1%	51.1%	0.90(0.60-1.36)P = 0.63
Intubation	117/283(41.3%)	612/5014(12.4%)	2.15(1.78-2.59)P<0.01	44.9%	31.9%	1.74(0.32- 9.58)P = 0.53
Patients with Chronic Kidney Diseases at Baseline						
	TocilizumabN=152	**ControlN= 3,343**	**HR(95% CI)p-value**	**Tocilizumab**	**Control**	**HR(95% CI)p-value**
Hospital Mortality	69/152(45.4%)	1071/3343(32.0%)	0.83(0.76-0.92)P <0.01	49.7%	46.1%	0.80(0.26 -2.46)P =0.70
Intubation	27/67(40.3)	190/1719(11.1%)	1.67(1.14-2.43)P<0.01	42.5%	29.6%	1.67(0.14-19.3)P = 0.68

*Patients on mechanical ventilation during the baseline period were excluded from the analysis. N, Number, HR, Hazard Ratio, CI, Confidence Interval.

vestigators et al., 2021). In this trial, more than half of the patients were on either high-flow nasal oxygen or non-invasive mechanical ventilation. Only 29.4% of patients were intubated at the time of randomization. This finding was consistent with one of the previous retrospective studies (Gupta et al., 2021). Unfortunately, as the timing of ICU admission was not available in our dataset, we were not able to replicate the exact inclusion criteria used in REMAP-CAP (REMAP-CAP Investigators et al., 2021). Furthermore, data from the RECOVERY trial indicated a statistically significant 28-day mortality benefit of the administration of TCZ group compared to standard of care (29% vs. 33%, respectively). This effect was more evident in patients receiving corticosteroids but not seen in patients who were on corticosteroids at baseline (Abani et al., 2021). Interestingly, patients who were not on invasive mechanical ventilation also benefited compared to those on mechanical ventilation. Thus, the timing of TCZ initiation (in instances with rapidly worsening respiratory status with/without high C-reactive protein levels) seems to be the important factor to maximize the benefit of TCZ (Abani et al., 2021, Sinha et al. 2020). Considering the heterogeneous population in our dataset, it was challenging to address the timing of TCZ administration in the course of COVID-19, especially at the acute progression of the disease. Thus, we included patients who only received tocilizumab within five days after admission to prevent the study of patients in the later stage of the disease where the drug may not produce any positive effect. Our analysis in patients with a high amount of supplementary non-invasive oxygen supports (such as those using BIPAP or oxygen masks) also showed a better short-term trend (Figure 2-A and B), although it was not statistically significant in the overall analysis.

We also assessed the rate of intubation after TCZ use and, despite various subgroup analyses, none of the clinical scenarios chosen in our study identified a TCZ benefit. The EMPACTA trial was the first clinical trial that showed some positive benefits of TCZ. Indeed, patients treated with TCZ were 44% less likely to progress to mechanical intubation or death by day 28. (HR 0.56, CI 0.32-0.97) (Salama et al., 2021). Furthermore, the REMAP-CAP used a composite outcome including invasive mechanical ventilation, ECMO, or death, which was significantly lower in the IL-6 inhibitor groups (Abani et al., 2021). However, other clinical trials did not replicate the findings consistent with the results of our study.

There are several limitations in our study. First, this is a de-identified database gathered from multiple centers in the U.S. De-identified databases have become one of the major sources of medical research, especially where the single-center study may not be able to reach the optimal sample size due to the rarity of the intervention or diseases. However, there were concerns in the veracity of de-identified data used in the previous studies in the past, which led to retraction of the studies (Mehra et al., 2020). Since then, the validity and trust of the data source have become paramount in studies using this kind of database. The Cerner Corporation is one of the leading electronic health record companies in the U.S. and has provided a de-identified electronic health record database for many years. Previously, it was called the Cerner Health Facts Deidentified Database and was recently updated as the Cerner Real World Data (CRWD) powered by Amazon Web Services Inc (AWS) (Corporation C). Second, this study is a retrospective study. Despite the size of the sample, the potential bias from the study design is inevitable. Although our study had a large number of patients, the interpretation requires significant caution. We collected various potential cofounders and successfully adjusted with a propensity score. The mode of oxygen delivery and PaO2/FiO2 ratio were used to control both groups for their oxygen requirement. The actual flow of oxygen was not used to control the groups as the interpretation is more complicated since the final concentration of oxygen depends on both the mode of oxygen delivery and the flow. We felt that PaO2/FiO2 is better indicator to demonstrate the severity of illness. Furthermore, the mortality rate of our cohort was higher than some randomized controlled

trials, such as the EMPACTA and COVACTA studies. (Rosas et al., 2021, Salama et al., 2021) Caution is needed in interpreting results. Lastly, infectious complications are one of the concerns in patients treated with TCZ. However, this matter was not evaluated in our study due to the unavailability of detailed microbiology data in the CRWD dataset.

Conclusion

Utilizing a large de-identified multicenter EHR database in the U.S., our study showed that, compared to a control group, TCZ use was not associated with improved mortality in patients hospitalized with COVID-19. However, survival curves did show a short-term trend towards better outcomes in the TCZ group. This positive trend was likely driven by the subgroup of patients who required a moderate amount of supplemental oxygen. The positive effects subsided in the long-term observation. The long-term benefits and risks of TCZ should also be carefully evaluated with follow-up studies.

Contributions

MN, AR: Data cleaning and preparation.
LR, SM, LL, DZ: Statistical analyses
MN, SK, BK, AH, CA, DZ: Manuscript preparation and review.

Conflict of Interest

All authors report no conflicts of interest related to this study.

Patient Consent Statement

The study was approved by the Institutional Review Board at the University of Texas Health Science center at Houston and patient consents are not required for this study.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2021.09.067.

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