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Infectious Complications After Tocilizumab in Patients with COVID: A Real-World Experience☆

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Abstract

Introduction: **Controversies remain regarding the safety of tocilizumab in the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. In this study, we seek to describe the infectious complications after tocilizumab in COVID patients and determine the related risk factors.**

Methods: **A single-center retrospective observational study was conducted among adult patients with SARS -CoV-2 infection admitted between 06/01/2020 and 12/31/2021 who received tocilizumab at our institution. Baseline demographics and laboratory values are obtained through reviewing electronic medical records. Risk factors of infectious complications after tocilizumab are identified through regression analysis. Statistics are performed using SPSS. P-value <0.05 is considered statistically significant.**

Results: **Out of the 52 patients identified, infectious complications after tocilizumab were documented in 30 patients (57.7%). The most common infections include pneumonia, urinary tract infections, and bacteremia of unknown sources. Overall mortality was 42.3%. Through multivariate regression analysis, age more than 65, hyperglycemia on admission, and tocilizumab administration more than 2 days after hospital admission are independent risk factors associated with developing infections.**

Conclusions: **In real-world experience, infectious complications are not uncommon in COVID patients who receive tocilizumab. Early use of tocilizumab may be of benefit. More rigorous patient selection and monitoring should be explored in future studies.**

Keywords: COVID-19, Tocilizumab, Interleukin-6 antagonist, Secondary infection, Complications of treatment

1. Introduction

Since its emergence in December 2019, SARS-CoV-2 has spread worldwide and continues to exert significant pressure on healthcare systems. Clinical manifestations range from self-limiting symptoms to acute respiratory distress syndrome (ARDS) and multi-organ failure. Markedly deranged inflammatory markers, elevated pro-inflammatory cytokines, including Interleukin-6 (IL-6), and profound coagulation abnormalities have been associated with severe cases.[1,2]

IL-6 is a cytokine with diverse physiologic roles in the inflammatory and immune responses to infection. Its dysregulation has been implicated in lymphoproliferative disorders and inflammatory conditions including other coronavirus infections (Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome).[3-5]

A previous study has linked elevated levels of pro-inflammatory cytokines with acute lung injury and, subsequently multi-organ dysfunction in SARS patients.[6] As a result, many studies have attempted to investigate the potential of IL-6 pathway blockade as a therapeutic strategy for COVID treatment. Tocilizumab is a monoclonal antibody against IL-6 receptor and has labeled indications for use in cytokine release syndromes. Early single-center

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experience from China[7,8] suggested clinical benefits associated with the use of tocilizumab, which has led to more rigorous examination of the evidence.

After the RECOVERY trial[9] and REMAP-CAP trial[10] were published, various professional societies, including National Institute of Health (NIH) and Infectious Disease Society of America (IDSA), have recommended tocilizumab as additional therapy in selected COVID populations. Here, in our hospital, tocilizumab is prescribed along with standard care in a case-by-case manner to COVID patients with rapid deterioration necessitating higher respiratory support. Although not observed initially in several randomized trials, infectious complications are not uncommon in our practice. Thus, in this study, we seek to describe the infectious complications after tocilizumab in COVID patients and determine the related risk factors.

2. Methods

We conducted a retrospective, observational study at a 528-bed tertiary community hospital in Rochester, New York. Medical records of adult patients (>18 years old) admitted between 06/01/2020 to 12/31/2021 with a polymerase chain reaction (PCR) confirmed SARS-CoV-2 infection were screened. Patients were selected if they received tocilizumab at our institution for the management of SARS-CoV-2. If a patient has more than one admission for COVID pneumonia, only the encounter with tocilizumab given was selected. The hospital Institutional Review Board has approved this study (IRB 2413A). Individual consent is waived.

2.1. Tocilizumab use

Institutional guidelines based on NIH and IDSA guidelines recommend consideration for tocilizumab on a case-by-case basis in conjunction with Infectious Disease and Pulmonary consultation. Potential criteria include hospitalized COVID-positive patients with severe disease (defined as SpO2 <90% on room air, respiratory rate >30 per minute, and/or signs of severe respiratory distress), who 1) require high flow nasal cannula (HFNC) 10L or more/non-invasive positive pressure ventilation (NIPPV), including continuous positive airway pressure and bilevel positive airway pressure/mechanical ventilation (MV) or 2) exhibit progressive increase of oxygen requirement despite remdesivir and dexamethasone. Patients need to have no evidence of active bacterial or fungal infection and are not on any immunomodulators other than corticosteroids. It is given as 8 mg/kg IV once.

2.2. Definition

Patients are considered to have infectious complications if, after tocilizumab, they received antibiotics from the primary team for the treatment of: a positive culture growing on a specimen from a sterile site; or positive culture from sputum sample, tracheal aspirate or bronchial alveolar lavage (BAL) excluding those samples in which pathogen quantity is rare and not further worked up by microbiology lab or if only Candida species is growing. Additionally, Patients are considered to have Clostridium Difficile (C diff) infection if in the presence of diarrhea, enzyme immunoassay is positive for both toxin and glutamate dehydrogenase (GDH) or if PCR is positive when the above two tests are discordant. If a patient had more than one level of oxygen support on a calendar day, the highest oxygen support on that calendar day is recorded. In case of nosocomial COVID infection, the day patient was tested positive for COVID was considered as day 1 of hospital admission.

2.3. Data

Demographic data collected include age, gender, ethnicity, body mass index, comorbidities and smoking status. Time intervals between COVID symptom onset, positive PCR result and hospital admission was recovered from individual documentations. Routine lab work, microbiology studies, daily oxygen support, antibiotic use, and COVID-specific treatment were also extracted from the electronic medical records. Primary outcome of interest is the incidence and risk factors for infectious complications after tocilizumab administration.

2.4. Statistical methods

Continuous variables are presented as median with interquartile range (IQR) or mean ± standard deviation. Categorical variables are presented as absolute numbers and percentages. Continuous variables are analyzed with non-parametric testing or student t-test as appropriate. The Chi-square test or Fisher exact test is used to compare categorical variables. Risk factors are identified through Logistic regression analysis. Statistics are performed using SPSS. P-value <0.05 is considered statistically significant.

3. Results

3.1. Baseline characteristics

A total of 52 patients were identified through chart review. Baseline characteristics are presented in Table 1. Median age was 63 years (IQR 51–73) and 28 (46.2%) were female. The median time from COVID diagnosis to hospital admission was 2 days (IQR 0–5). Tocilizumab was administered after a median of 3 days (IQR 1–6.5) after hospital admission (Table 1 and Fig. 1). Most patients (84.6%) were on HFNC or NIPPV on the day receiving tocilizumab. All patients received dexamethasone and most received remdesivir.

3.2. Clinical outcomes

Out of the cohort, 30 patients (57.7%) developed an infectious complication after tocilizumab. Compared with patients who did not have documented infections, those who did were significantly older (52 vs 68 years, $p = 0.001$) with a higher Charlson comorbidity index (1 vs 4, $p = 0.004$). They also more frequently had central venous access prior to tocilizumab infusion (9.1% vs 43%, $p = 0.014$), received tocilizumab later after hospital admission (1 vs 5 days, $p = 0.007$), or after a longer duration since COVID symptom onset (9.5 vs 14.5 days, $p = 0.004$), spent more days on HFNC, NIPPV or mechanical ventilation before receiving tocilizumab (2 vs 3 days, $p = 0.002$) and had longer hospital length of stay (14 vs 31 days, $p = 0.012$) (Table 1). Neither prior fever nor routine blood work reliably distinguish these two patient groups, however a tendency (3% vs 11%, $p = 0.074$) to exhibit hyperglycemia on admission (defined as random blood glucose more than 200 mg/dl) was observed in the infectious subgroup.

The median time from tocilizumab administration to developing infectious complications was 5.5 days (IQR 4–16) (Fig. 2). The most common infection was pneumonia (29 cases, representing 74% of all documented infections), followed by urinary tract infections (5 cases, 13%) and bacteremia of unknown sources (2 cases, 5%). Methicillin-sensitive *Staphylococcus aureus* (MSSA) and *Pseudomonas aeruginosa* were among the most common recovered pathogens, representing 21% and 19% respectively. There were 6 cases of multidrug-resistant bacterial infection (2 extended-spectrum β-lactamase (ESBL) producing Klebsiella, 1 ESBL producing E coli and 3 carbapenem-resistant Enterobacterales (CRE)) and 3 cases of invasive fungal infection (1 Candidemia and 2 invasive Aspergilloses). (Fig. 3).

Overall mortality was 42.3%. Median days alive after tocilizumab was 16.5 (IQR 9.8–26). Patients with infectious complications have higher mortality of 60% ($P = 0.003$). Compared with the patients who survived the hospitalization, those who died were older (72 vs 55 years, $P < 0.001$) with more comorbidities (Charlson Comorbidity Index, 4 vs 2, $P < 0.001$). Antibiotics were more frequently prescribed in these patients before receiving tocilizumab (40.9% vs 13.3%, $P = 0.023$) and they more often had documented infectious complications after tocilizumab administration (81.8% vs 40%, $P = 0.003$).

To explore risk factors for developing infectious complications, regression analysis are performed with results summarized in Table 2. Age more than 65, hyperglycemia on admission, and tocilizumab administration more than 2 days after hospital admission are independently associated with developing infections.

4. Discussion

In this retrospective study, a high rate of infectious complications (57.7%) was observed in COVID patients who received tocilizumab. We were also able to identify several independent risk factors, which include older age, late use of tocilizumab, and hyperglycemia on admission.

This patient cohort is similar to previously published literature, with the median age in the early 60s and Diabetes and cardiovascular disease being the most common comorbidities. Pneumonia was the most common infectious complication identified, representing 74% of infectious cases. This is similar to the 61.9% described by Rajendram et al.[11] at Cleveland Clinic and 45% by Somers et al.[12] from University of Michigan. Even though this study relied on the primary team's decision to treat, this still may underestimate the true infection rates. A subset of 6 patients who were suspected of having an infection and were treated with antibiotics but never had a positive culture were excluded from infection group. Furthermore, patients who were started on antibiotics prior to obtaining cultures may have higher false-negative culture results.

Nonetheless, the incidence of infectious complications observed in our study is higher than in published randomized trials. Infection rates after tocilizumab in the literature range from 1 in 353 cases reported in REMAP-CAP trial[10] to 1.7% in RCT-TCZ-COVID trial[13] and 8% in BACC BAY trial[14] to 33.3% in REMDACTA trial[15] and 38.3% in COVACTA trial.[16] This variability may be related to the variability in the timing of tocilizumab

Table 1. Baseline characteristics and clinical parameters.

	Total cohort (n = 52)	No infectious complications (n = 22)	With infectious complications (n = 30)	P value
Age (years)	63 (51.2–72.8)	52 (35–64.8)	68 (62.5–74.3)	0.001
Body mass index (BMI)	34.5 ± 7.1	33.6 ± 6.8	34.5 ± 8.0	0.725
Charlson comorbidity index	3 (1–5)	1 (0–3.5)	4 (2–5)	0.004
Female	28 (53.8%)	13 (59.1%)	15 (50)	0.516
Ethnicity				0.342
Caucasian	25 (48.1%)	8 (36.4%)	17 (56.7%)	
African American	16 (30.8%)	7 (31.8%)	9 (30%)	
Hispanic	9 (17.3%)	6 (27.3%)	3 (10%)	
Other	2 (3.8%)	1 (4.5%)	1 (3.3%)	
Smoking status				0.222
Active smoker	6 (11.5%)	1 (4.5%)	5 (16.7%)	
Former smoker	17 (32.7%)	6 (27.3%)	11 (36.7%)	
Non smoker	29 (55.8%)	15 (68.2%)	14 (46.7%)	
Comorbidities				
Diabetes	23 (44.2%)	8 (36.4%)	15 (50%)	0.328
Hypertension	33 (63.5%)	8 (36.4%)	25 (83.3%)	0.001
Hyperlipidemia	26 (50%)	8 (36.4%)	18 (60%)	0.092
Chronic kidney disease	14 (26.9%)	3 (13.6%)	11 (36.7%)	0.064
Dialysis	1 (1.9%)	0 (0%)	1 (3.3%)	[b]
Coronary artery disease	6 (11.5%)	2 (9.1%)	4 (13.3%)	[b]
COPD/asthma	18 (34.6%)	8 (36.4%)	10 (33.3%)	0.820
Congestive heart failure	6 (11.5%)	1 (4.5%)	5 (16.7%)	[b]
Malignancy	9 (17.3%)	3 (13.6%)	6 (20%)	[b]
Venous thromboembolism	2 (3.8%)	0 (0%)	2 (6.7%)	[b]
Immunosuppression	4 (7.7%)	1 (4.5%)	3 (10%)	[b]
Hospital admission after covid diagnosis (days)	2 (0–5)	2.5 (1–6.3)	2 (0–5)	0.128
Tocilizumab administration after hospital admission (days)	3 (1–6.75)	1 (1–4)	5 (1–9)	0.007
Tocilizumab administration after symptom onset (days)	13 (8–16)	9.5 (5–13)	14.5 (11.5–17.25)	0.004
Lab work				0.499
WBC count on admission (109/L)	8.0 ± 3.8	8.5 ± 4.3	7.6 ± 3.4	0.845
Lymphocyte/neutrophil on admission	0.19 ± 0.19	0.18 ± 0.20	0.20 ± 0.29	0.745
CRP on admission (mg/dl)	131 (101–191)	125 (103–176)	137 (88–196)	0.541
Ferritin on admission (ng/ml)	863 (495.8–1392)	663 (408–1384)	1103 (521–1490)	0.670
LDH on admission (U/l)	505 ± 212	525 ± 230	491 ± 201	0.243
WBC count on day of tocilizumab administration (109/L)	10.5 ± 4.9	9.2 ± 4.4	11.4 ± 5.1	0.773
CRP on day of tocilizumab administration	127 (101–183)	113 (59–151)	131 (102–200)	
Glycemic control				
Hyperglycemia on admission	14 (26.9%)	3 (13.6%)	11 (36.7%)	0.074
Morning blood glucose on day of tocilizumab (mg/dl)	191.4 ± 89.0	162.4 ± 40.8	209.8 ± 105.8	0.234
Fever within 24h prior to tocilizumab administration	14 (26.9%)	6 (27.3%)	8 (26.7%)	0.961
Antibiotic exposure prior to tocilizumab after ED admission	13 (25%)	3 (13.6%)	10 (33.3%)	0.115
Central access prior to tocilizumab	15 (28.8%)	2 (9.1%)	13 (43.3%)	0.014
Respiratory support on day of tocilizumab administration				[b]
Nasal cannula, oxymask, non-rebreather	1 (1.9%)	1 (4.5%)	0 (0%)	
HFNC or NIPPV	44 (84.6%)	19 (86.4%)	25 (83.3%)	
Mechanical ventilation	7 (13.5%)	2 (9.1%)	5 (16.7%)	
Duration of nasal cannula before tocilizumab (days)	1 (0–3)	1 (0–2)	2 (0–3)	0.084
Duration of HFNC, NIPPV or mechanical ventilation before tocilizumab (days)	2 (1–4.75)	2 (1–2)	3 (2–8)	0.002
Antibiotic use on the day prior to obtaining any culture after tocilizumab[a]	16 (35.6%)	4 (30.7%)	12 (40%)	0.378
Death in hospital	22 (42.3%)	4 (18.2%)	18 (60%)	0.003
Length of stay (days)	22.5 (14–38.5)	14 (8.8–25)	31 (18.5–59.3)	0.012

[a] No culture was obtained in 7 patients after receiving tocilizumab.
[b] P value is not calculated due to low incidence rate.

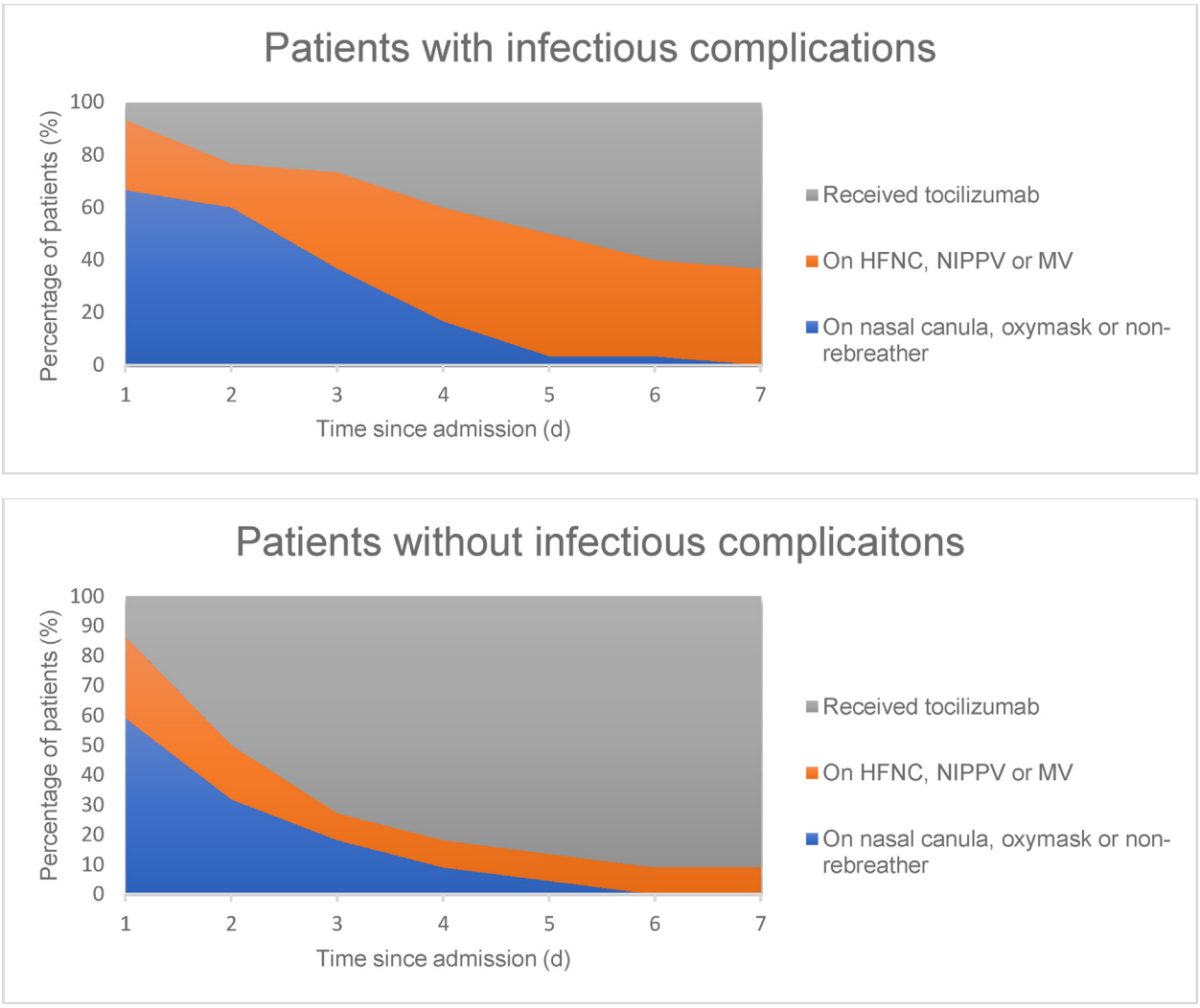

Fig. 1. Daily oxygen support and tocilizumab administration during the first week of admission. (On a certain calendar day, patients who have received tocilizumab are represented in the gray area. Patients who have not received tocilizumab are represented in the orange or blue area depending on the level of oxygen support on that calendar day).

administration relative to symptom and hospitalization duration. In the REMAP-CAP trial, which describes the lowest rate of infectious complications and the largest benefits associated with tocilizumab, patients were enrolled after a median of 1.2 days since hospital admission and a median of 13 h since ICU admission. In the BACC BAY trial, patients were enrolled after a median of 9 days since symptom onset and within 72 h of clinical worsening. In the COVACTA trial, which identifies a higher risk of infectious complications, patients were enrolled after a mean of 12 days since symptom onset and a median of 5 days from mechanical ventilation. In our study, the median time of tocilizumab administration is 13 days (IQR 8–16) from symptom onset and 3 days (IQR 1–6.75) from hospital admission. Observed infection rates were high, but it is close to the range reported in the COVACTA trial, which also enrolls patients relatively late in the course.

As seen in Fig. 1, patients with documented infections tend to deteriorate and receive tocilizumab late. We propose that the timing of tocilizumab administration can potentially determine the benefit derived from blocking the cytokine storm. While there's no prospective trial investigating the importance of timing, retrospective studies have focused on its effects. Several studies are able to identify a potential relationship between lower mortality and early use of tocilizumab, although the definition of "early" varies (for example, within 24 h after hospital admission in[17], within 12 days of symptom onset in[18], or at the inflammatory stage in[19]). One particular study in Northwell Health

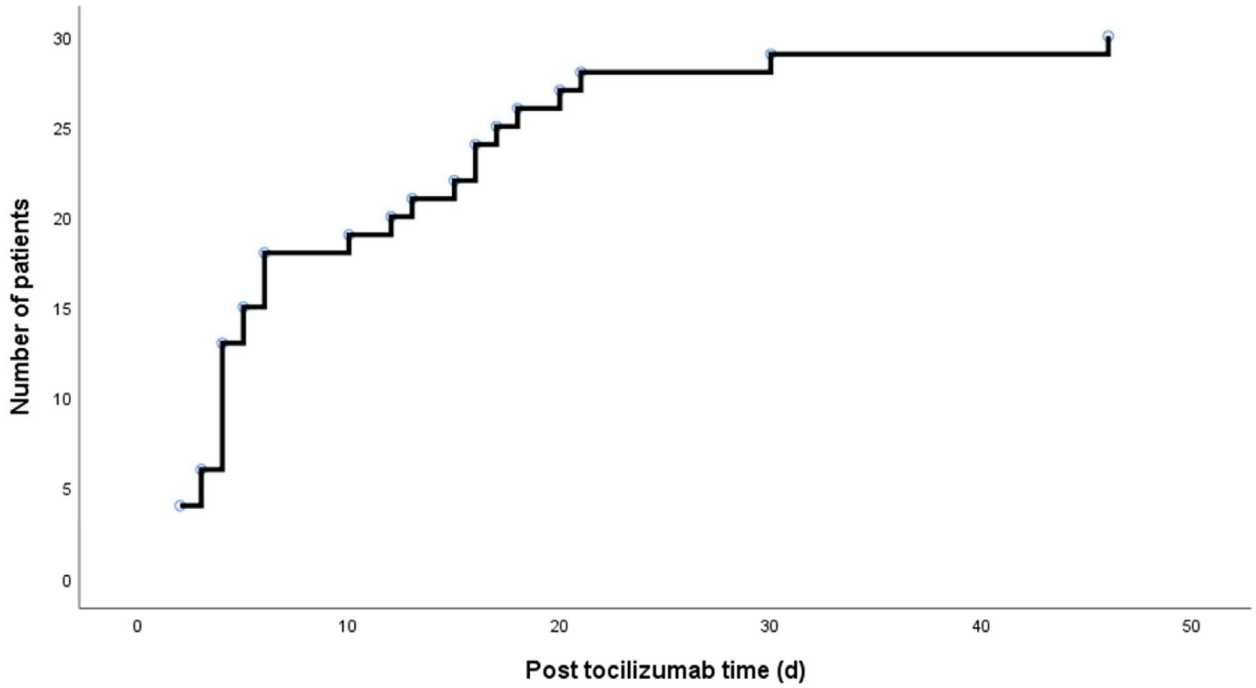

Fig. 2. Timing of discovering infections after tocilizumab administration.

System enrolling more than 11,000 patients[20] showed there was a consistent suggestion of a trend of increasing mortality with each day's delay in tocilizumab administration at all level of oxygen requirements.

Two potential mechanisms may explain why there may be less benefit of tocilizumab when used late in the disease course:

The first mechanism may be that there's a point in time when the inflammatory cascade is too advanced to benefit from tocilizumab's IL-6 inhibition. As proposed by Angriman et al.,[21] the peak of inflammatory response to SARS-CoV-2 often coincides with or shortly precedes clinical deterioration, and once the inflammatory cascade achieves a state of hyperactivity, it may be too late to intervene.

The second mechanism is that patients who deteriorate late can represent a different subset of patients, some of whom may already have unrecognized infections at the time of tocilizumab administration. In the study of Pickens et al.,[22] when routine early bronchoalveolar lavage is performed after intubation, 21.1% of COVID patients have superimposed bacterial pneumonia at the time of intubation, but neither standard clinical measures (including baseline characteristics, maximum temperature, antibiotics use et al.) nor blood biomarkers can identify this patient subgroup. Consequently, rather than COVID itself, some of the late deteriorating patients may have deterioration due to unrecognized superimposed infection despite best clinical judgment. Indeed, in an observational study exploring patterns of deterioration,[23] COVID patients tend to have a short phase of respiratory distress (median 3 days) before developing severe ARDS requiring mechanical ventilation.

However, due to this study's retrospective nature, such a hypothesis cannot be readily tested. Although we acknowledge that retrieving the time of symptom onset and resources regarding testing and admission can be heterogeneous in an individual patient, further subgroup analysis of prospective trials or individual-level metanalysis might be a good starting point to evaluate the effects of timing.

We also observed that hyperglycemia on admission is an independent risk factor for having infectious complications. Diabetes and uncontrolled hyperglycemia have been associated with worse outcomes in COVID patients.[24-26] In a retrospective study reviewing glycemic control, the mortality rate was 28.7% in patients with diabetes or uncontrolled hyperglycemia compared with 6.2% in patients without either.[25] Several different mechanisms have been postulated regarding COVID and hyperglycemia: severe inflammatory response to the virus,[26] suppressed function of pancreatic beta cells,[27] and corticosteroid use. However, without prospective studies, it is hard to determine if hyperglycemia is a

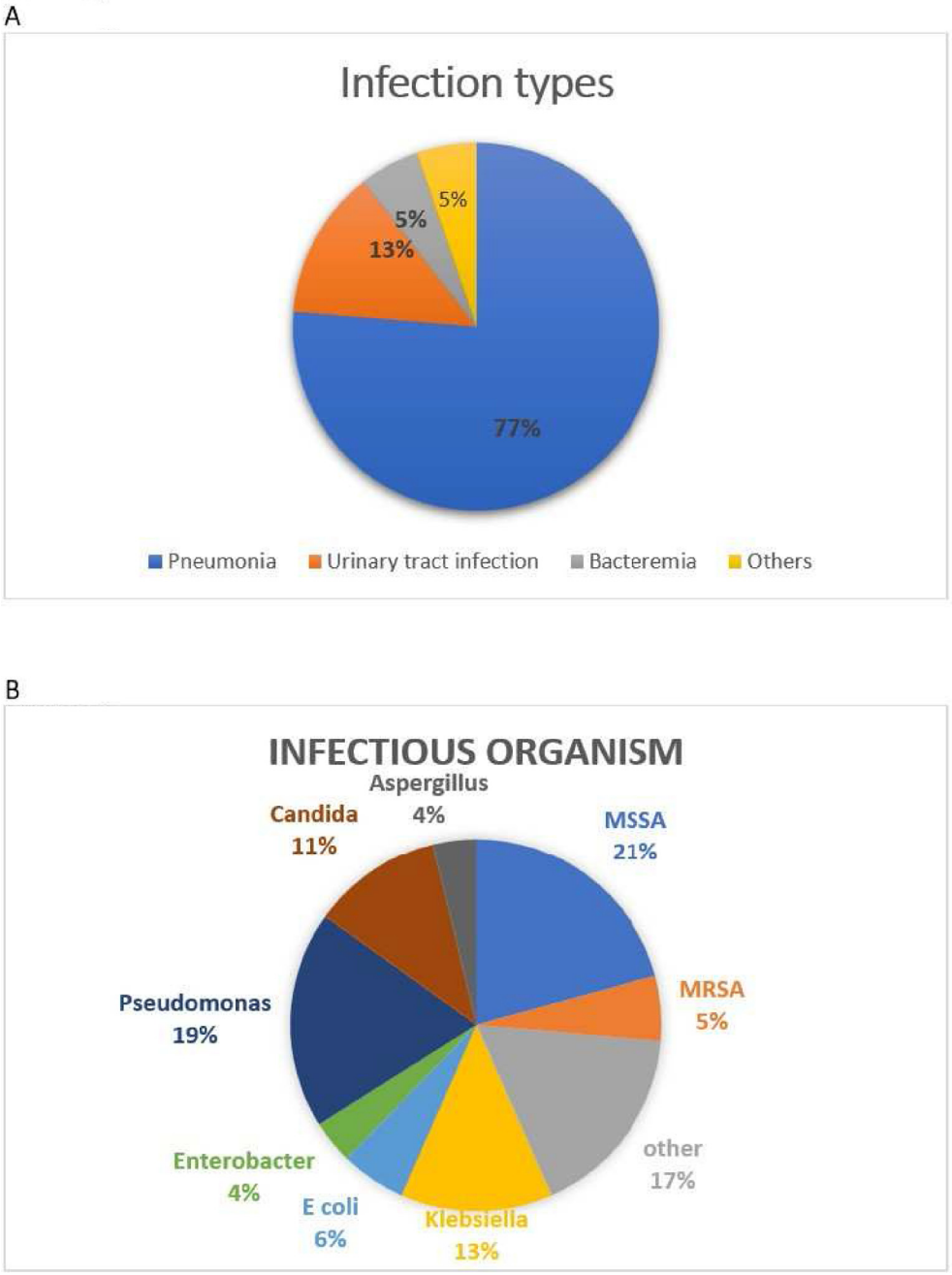

Fig. 3. Infectious complications after tocilizumab according to the site of infection (3A) and recovered organisms (3B). Others in A include a case of empyema and a case of C diff colitis. Others in B include Clostridium difficile, Proteus species, Stenotrophomonas maltophilia, Serratia marcescens, Eikenella corrodens, Haemophilus influenza, Streptococcus species, Chryseobacterium indologenes (MSSA, methicillin-sensitive Staphylococcus Aureus, MRSA, methicillin-resistant Staphylococcus Aureus, E coli, Escherichia coli).

cause or a consequence of severe disease. Whether glycemic control leads to clinical benefit needs to be further explored.

4.1. Limitations

The limitations of current study are several-fold. First, the retrospective nature of our study limits the causative conclusions that can be drawn due to potential unaccounted confounding factors. Per our institutional guideline, all patients with severe COVID disease were considered for tocilizumab unless there was a contraindication. Due to the existence of selection bias, infection risk in those patients with severe disease who did not receive tocilizumab was not collected and thus we were not

Table 2. Univariate and multivariate binary regression analysis of risk factors for developing infectious complications after tocilizumab.

Variables	Univariate analysis			Multivariate analysis		
	Odds Ratio	95% confidence interval	P value	Odds ratio	95% confidence interval	P value
Age >65	6.800	1.942–23.810	0.003	4.618	1.083–19.695	0.039
Chalson comorbidity index >3	3.886	1.138–13.271	0.030			
Central access before tocilizumab	7.647	2.509–38.759	0.014			
Antibiotics exposure before tocilizumab	3.167	0.754–13.279	0.115			
Hyperglycemia on admission	3.667	0.881–15.284	0.074	6.881	1.180–40.131	0.032
Tocilizumab >2 days after admission	7.333	2.214–25.316	0.002	6.543	1.488–28.698	0.013
Tocilizumab >2 days after requiring HFNC, NIPPV or mechanical ventilation	13.077	2.580–66.280	0.002			

able to discern the effect of tocilizumab on infectious complications. Second, this is a single-center experience. Certain practice styles and clinical resources may limit the generalizability of the results. Third, most patients in our cohort were on HFNC or NIPPV at the time of tocilizumab administration. Infectious complications in patients on other modalities of respiratory support cannot be readily inferred. Fourth, our study focuses on identifying risk factors for developing infectious complications. The best surveillance method for patients with such risk factors is beyond the scope of our current study.

5. Conclusions

In real-world experience, infectious complications are not uncommon in COVID patients who receive tocilizumab. Age more than 65, administration of tocilizumab more than 2 days after hospital admission, and hyperglycemia on admission are independent risk factors for developing infectious complications. Early use of tocilizumab may be of benefit. More rigorous patient selection and monitoring should be explored in future studies.

Disclaimers

This article has not been submitted to other publications and/or Part of the study was represented at CHEST 2022 annual conference.

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Conflict of interest

Authors declare no conflict of interest exists.

References

1. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet (London, England)*. Mar 28 2020;395(10229):1033–1034. https://doi.org/10.1016/s0140-6736(20)30628-0.
2. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemostasis : JTH*. Apr 2020;18(4):844–847. https://doi.org/10.1111/jth.14768.
3. Garbers C, Heink S, Korn T, Rose-John S. Interleukin-6: designing specific therapeutics for a complex cytokine. *Nature reviews Drug discovery*. Jun 2018;17(6):395–412. https://doi.org/10.1038/nrd.2018.45.
4. Zhang Y, Li J, Zhan Y, et al. Analysis of serum cytokines in patients with severe acute respiratory syndrome. *Infect Immun*. Aug 2004;72(8):4410–4415. https://doi.org/10.1128/iai.72.8.4410-4415.2004.
5. Lau SKP, Lau CCY, Chan KH, et al. Delayed induction of proinflammatory cytokines and suppression of innate antiviral response by the novel Middle East respiratory syndrome coronavirus: implications for pathogenesis and treatment. *J Gen Virol*. Dec 2013;94(Pt 12):2679–2690. https://doi.org/10.1099/vir.0.055533-0.
6. He L, Ding Y, Zhang Q, et al. Expression of elevated levels of pro-inflammatory cytokines in SARS-CoV-infected ACE2+ cells in SARS patients: relation to the acute lung injury and pathogenesis of SARS. *The Journal of pathology*. Nov 2006;210(3):288–297. https://doi.org/10.1002/path.2067.
7. Luo P, Liu Y, Qiu L, Liu X, Liu D, Li J. Tocilizumab treatment in COVID-19: a single center experience. *J Med Virol*. Jul 2020;92(7):814–818. https://doi.org/10.1002/jmv.25801.
8. Xu X, Han M, Li T, et al. Effective treatment of severe COVID-19 patients with tocilizumab. *Proc Natl Acad Sci USA*. May 19 2020;117(20):10970–10975. https://doi.org/10.1073/pnas.2005615117.
9. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet (London, England)*. May 1 2021;397(10285):1637–1645. https://doi.org/10.1016/s0140-6736(21)00676-0.
10. Gordon AC, Mouncey PR, Al-Beidh F, et al. Interleukin-6 receptor antagonists in critically ill patients with covid-19. *N Engl J Med*. Apr 22 2021;384(16):1491–1502. https://doi.org/10.1056/NEJMoa2100433.
11. Rajendram P, Sacha GL, Mehkri O, et al. Tocilizumab in coronavirus disease 2019-related critical illness: a propensity matched analysis. Critical care explorations. Jan 2021;3(1), e0327. https://doi.org/10.1097/cce.0000000000000327.
12. Somers EC, Eschenauer GA, Troost JP, et al. Tocilizumab for treatment of mechanically ventilated patients with COVID-19. *Clin Infect Dis : an official publication of the Infectious Diseases Society of America*. Jul 15 2021;73(2):e445–e454. https://doi.org/10.1093/cid/ciaa954.

13. Salvarani C, Dolci G, Massari M, et al. Effect of tocilizumab vs standard care on clinical worsening in patients hospitalized with COVID-19 pneumonia: a randomized clinical trial. *JAMA Intern Med*. Jan 1 2021;181(1):24–31. https://doi.org/10.1001/jamainternmed.2020.6615.
14. Stone JH, Frigault MJ, Serling-Boyd NJ, et al. Efficacy of tocilizumab in patients hospitalized with covid-19. *N Engl J Med*. Dec 10 2020;383(24):2333–2344. https://doi.org/10.1056/NEJMoa2028836.
15. Rosas IO, Diaz G, Gottlieb RL, et al. Tocilizumab and remdesivir in hospitalized patients with severe COVID-19 pneumonia: a randomized clinical trial. *Intensive care medicine*. Nov 2021; 47(11):1258–1270. https://doi.org/10.1007/s00134-021-06507-x.
16. Rosas IO, Bräu N, Waters M, et al. Tocilizumab in hospitalized patients with severe covid-19 pneumonia. *N Engl J Med*. Apr 22 2021;384(16):1503–1516. https://doi.org/10.1056/NEJMoa2028700.
17. San-Juan R, Fernández-Ruiz M, López-Medrano F, et al. Analysis of the factors predicting clinical response to tocilizumab therapy in patients with severe COVID-19. *Int J Infect Dis: Int J Infect Dis: official publication of the International Society for Infectious Diseases*. Apr 2022;117:56–64. https://doi.org/10.1016/j.ijid.2022.01.040.
18. Eşkazan AE, Balkan İ, Demirbaş KC, et al. Tocilizumab in COVID-19: the cerrahpaşa-PREDICT score. *J Infect Chemother: official journal of the Japan Society of Chemotherapy*. Sep 2021; 27(9):1329–1335. https://doi.org/10.1016/j.jiac.2021.05.007.
19. Durán-Méndez A, Aguilar-Arroyo AD, Vivanco-Gómez E, et al. Tocilizumab reduces COVID-19 mortality and pathology in a dose and timing-dependent fashion: a multi-centric study. *Sci Rep*. Oct 5 2021;11(1):19728. https://doi.org/10.1038/s41598-021-99291-z.
20. Singh AK, Oks M, Husk G, et al. Impact of timing of tocilizumab use in hospitalized patients with SARS-CoV-2 infection. *Respir Care*. Dec 2021;66(12):1805–1814. https://doi.org/10.4187/respcare.08779.
21. Angriman F, Ferreyro BL, Burry L, et al. Interleukin-6 receptor blockade in patients with COVID-19: placing clinical trials into context. *Lancet Respir Med*. Jun 2021;9(6):655–664. https://doi.org/10.1016/s2213-2600(21)00139-9.
22. Pickens CO, Gao CA, Cuttica MJ, et al. Bacterial superinfection pneumonia in patients mechanically ventilated for COVID-19 pneumonia. *Am J Respir Crit Care Med*. Oct 15 2021;204(8):921–932. https://doi.org/10.1164/rccm.202106-1354OC.
23. Chen SL, Feng HY, Xu H, et al. Patterns of deterioration in moderate patients with COVID-19 from jan 2020 to mar 2020: a multi-center, retrospective cohort study in China. *Front Med*. 2020;7:567296. https://doi.org/10.3389/fmed.2020.567296.
24. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese center for disease control and prevention. *Jama*. Apr 7 2020;323(13):1239–1242. https://doi.org/10.1001/jama.2020.2648.
25. Bode B, Garrett V, Messler J, et al. Glycemic characteristics and clinical outcomes of COVID-19 patients hospitalized in the United States. *Journal of diabetes science and technology*. Jul 2020;14(4):813–821. https://doi.org/10.1177/1932296820924469.
26. Zhu L, She ZG, Cheng X, et al. Association of blood glucose control and outcomes in patients with COVID-19 and preexisting type 2 diabetes. *Cell Metabol*. Jun 2 2020;31(6): 1068–1077e3. https://doi.org/10.1016/j.cmet.2020.04.021.
27. Yang L, Han Y, Nilsson-Payant BE, et al. A human pluripotent stem cell-based platform to study SARS-CoV-2 tropism and model virus infection in human cells and organoids. *Cell Stem Cell*. Jul 2 2020;27(1):125–136e7. https://doi.org/10.1016/j.stem.2020.06.015.