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Contents

Bimonthly Volume 10 Number 5 September 9, 2021

OPINION REVIEW

REVIEW

MINIREVIEWS

ORIGINAL ARTICLE

Case Control Study

Observational Study

SYSTEMATIC REVIEWS

World Journal of Critical Care Medicine

Bimonthly Volume 10 Number 5 September 9, 2021

Contents

World Journal of Critical Care Medicine

Bimonthly Volume 10 Number 5 September 9, 2021

Contents

ABOUT COVER

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AIMS AND SCOPE

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WJCCM mainly publishes articles reporting research results and findings obtained in the field of critical care medicine and covering a wide range of topics including acute kidney failure, acute respiratory distress syndrome and mechanical ventilation, application of bronchofiberscopy in critically ill patients, cardiopulmonary cerebral resuscitation, coagulant dysfunction, continuous renal replacement therapy, fluid resuscitation and tissue perfusion, hemodynamic monitoring and circulatory support, ICU management and treatment control, sedation and analgesia, severe infection, *etc.*

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ORIGINAL ARTICLE

Observational Study

Retrospective analysis of anti-inflammatory therapies during the first wave of COVID-19 at a community hospital

Jose I Iglesias, Andrew V Vassallo, Jesse B Sullivan, Yasmine Elbaga, Vishal V Patel, Nikunjkumar Patel, Lydia Ayad, Payam Benson, Marina Pittiglio, Emad Gobran, Alexander Clark, Wajahat Khan, Kaliope Damalas, Rajesh Mohan, Satyendra P Singh

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Institutional review board statement: The study was approved by the Community Medical Center Institutional

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Abstract

BACKGROUND

Our understanding of the severe acute respiratory syndrome coronavirus 2 has evolved since the first reported cases in December 2019, and a greater emphasis has been placed on the hyper-inflammatory response in severely ill patients. The

Review Board (IRB # 20-005).

Informed consent statement: Informed consent was waived by the Community Medical Center Institutional Review Board as the study was deemed minimal risk to participants due to its retrospective nature and de-identified results.

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purpose of this study was to determine risk factors for mortality and the impact of anti-inflammatory therapies on survival.

AIM

To determine the impact of various therapies on outcomes in severe coronavirus disease 2019 patients with a focus on anti-inflammatory and immune-modulating agents.

METHODS

A retrospective analysis was conducted on 261 patients admitted or transferred to the intensive care unit in two community hospitals between March 12, 2020 and June 17, 2020. Totally 167 patients received glucocorticoid (GC) therapy. Seventy-three patients received GC alone, 94 received GC and tocilizumab, 28 received tocilizumab monotherapy, and 66 received no anti-inflammatory therapy.

RESULTS

Patient survival was associated with GC use, either alone or with tocilizumab, and decreased vasopressor requirements. Delayed administration of GC was found to decrease the survival benefit of GC therapy. No difference in survival was found with varying anticoagulant doses, convalescent plasma, tocilizumab monotherapy; prone ventilation, hydroxychloroquine, azithromycin, or intravenous ascorbic acid use.

CONCLUSION

This analysis demonstrated the survival benefit associated with anti-inflammatory therapy of GC, with or without tocilizumab, with the combination providing the most benefit. More studies are needed to assess the optimal timing of anti-inflammatory therapy initiation.

Key Words: COVID-19; Corticosteroids; Intensive care unit; Methylprednisolone; Tociluzimab; Anti-inflammatory

Core Tip: Anti-inflammatory therapy with glucocorticoids (including methylprednisolone) and combination treatment with tocilizumab and glucocorticoids improve survival in critically ill patients with coronavirus disease 2019. Dual inhibition of the NFK-β therapy with glucocorticoid and inhibition of the interleukin-6 pathway with tocilizumab may offer greater survival benefits.

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INTRODUCTION

In late December 2019, patients in Wuhan, China began presenting to hospitals with a viral pneumonia of unknown origin characterized by a clinical syndrome comprising of cough and dyspnea[1,2]. While there was a wide range of severity, the disease could lead to respiratory failure and death. Caused by the coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), this disease state was named the coronavirus disease 2019 (COVID-19). Following rapid international spread, the World Health Organization upgraded the outbreak to a pandemic, the first pandemic since the 2009 H1N1 outbreak[3]. As of January 29, 2021, the disease has over 100 million cases confirmed infections and over 2 million confirmed deaths[4]. Our understanding of the disease state has continued to evolve as well. While the high mortality rate was

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originally thought to be closely related to acute respiratory distress syndrome (ARDS), newer evidence has shown additional potential causes[5]. Severely ill patients may have a hyper immune response, leading to dysregulated and excessive cytokine release which can lead to multiple-organ failure[6]. Patients have been found to enter a hypercoagulable state, leading to increased risk of thrombosis and strokes[7,8]. Our better understanding and continued research has led to rapid changes in treatment recommendations for COVID-19.

Treatment for COVID-19 has been rapidly evolving as new evidence emerges. Therapies have focused on antivirals (*e.g.*, remdesivir, favipiravir), anti-inflammatory medications (dexamethasone, methylprednisolone), antibodies (convalescent plasma), immunotherapy (tocilizumab, anakinra, sarilumab), anticoagulation (heparin), vitamin therapy (ascorbic acid, vitamin D), different modalities of respiratory support, and other novel therapies (hydroxychloroquine, melatonin, famotidine)[9]. Remdesivir, an antiviral therapy, was the first approved therapy to treat COVID-19 in hospitalized patients aged 12 and older weighing at least 40 kg. Remdesivir shows in-vitro activity against SARS-CoV-2 as well as a quicker time to recovery in hospitalized COVID-19 patients[10-13].

Immune based therapies have theoretical benefits in the cytokine storm phase of the disease. Corticosteroids have been employed due to their potent anti-inflammatory and immunomodulatory effects. Dexamethasone showed favorable clinical results in COVID-19 in the RECOVERY trial, demonstrating a lower 28-d mortality in patients receiving invasive mechanical ventilation or oxygen alone[14]. Patients who did not require supplemental oxygen did not benefit from the addition of dexamethasone. A meta-analysis of 7 randomized controlled trials that included hydrocortisone, methylprednisolone, and dexamethasone showed lower 28-d all-cause mortality, however the majority of data came from the RECOVERY trial[15]. The METCOVID trial was a parallel, double-blind, placebo-controlled, randomized clinical trial which compared methylprednisolone *vs* placebo in hospitalized patients with COVID-19[16]. The primary endpoint of 28 d mortality was not different between groups, however a post-hoc analysis of the data demonstrated that patients > 60 years old who received methylprednisolone did have decreased 28 d mortality.

Some concerns remain over using corticosteroids to treat COVID-19. Data from other novel coronavirus infectious, namely Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS) show a negative effect on virus clearance with steroid use[17,18]. Liu *et al*[19] showed negative effects of corticosteroids in COVID-19 including increased 28-d mortality and delayed viral clearance in a large multicenter retrospective analysis. Methylprednisolone made up the majority (96.8%) of the steroids used.

Tocilizumab is a monoclonal antibody which competitively inhibits the action of interleukin-6 (IL-6), a pro-inflammatory cytokine which correlates with disease severity in COVID-19[20,21]. Tocilizumab has shown mixed results in randomized clinical trials. Earlier trials used tocilizumab as mostly monotherapy with low utilization of corticosteroids and failed to show efficacy[22-25]. Later trials, such the REMAP CAP and RECOVERY trials, utilized corticosteroids in greater numbers due to the release of the RECOVERY trial data on dexamethasone, and showed decreased mortality with tocilizumab[26,27]. The RECOVERY trial included only patients with C-reactive protein (CRP) > 75 mg/L, while the REMAP CAP trial did not specify a CRP threshold for inclusion, but found the strongest effect in the subgroup with highest CRP.

MATERIALS AND METHODS

Study population and data collection

To determine risk factors for mortality and the impact of anti-inflammatory therapy on survival in patients critically ill from COVID-19 we conducted a retrospective analysis of 261 consecutive patients admitted or transferred to the intensive care unit (ICU) of two community hospitals from March 12th to June 17th 2020. The study was approved by the Community Medical Center Institutional Review Board (IRB # 20-005). Inclusion criteria were the following: confirmed diagnosis of SARS-CoV-2 (COVID-19) by a positive PCR test and signs and symptoms of COVID-19 infection, age greater than 18. The study baseline was the time of hospital admission. In terms of ICU management, patients received standard of care therapy. Management and timing of ventilator support, employment of ARDS net ventilator strategies, antibiotic use, antiviral therapy, use of anticoagulation, initiation of vasopressors, use of convalescent

plasma, glucocorticoid (GC) therapy (defined as GC use for greater than 48 h), and use of tocilizumab was determined by the ICU physician and consultants.

Patient demographics, comorbidities, clinical and outcome variables were obtained from the electronic medical record and entered into a de-identified database. Measurements included arterial blood gas, routine metabolic chemistries, CRP, D-Dimer, IL-6, ferritin, complete blood count with differential, and all variables necessary to calculate the Sequential Organ Failure Assessment (SOFA) score on admission. Other collected data included the day of admission, date of ICU transfer, date of death, length of vasopressor usage, days on mechanical ventilation, partial pressure of oxygen to fraction inspired of oxygen (PaO_2/FIO_2) ratio, time to initiation of GC therapy, time to ICU transfer, use of therapeutic agents [azithromycin, hydroxychloroquine, convalescent plasma, use of heparin (low molecular weight or unfractionated either as prophylaxis or full anticoagulant therapy), and use of tocilizumab].

Acute kidney injury (AKI) was defined based on kidney disease: Improving Global Outcomes criteria; namely, an increase in serum creatinine (SCr) > 0.3 mg/dL or a level > 1.5 times the baseline value SCr by ≥ 0.3 mg/dL, within 48 h. Where SCr at baseline is unknown and there is no documented history of chronic kidney disease baseline SCr was arbitrarily assigned a value of 1 mg/dL[28]. Timing and indication for the initiation of renal replacement therapy were determined by the consulting nephrologist.

Ethics statement

All procedures performed in the study were in accordance with the 1964 Helsinki declaration and its later amendments. Patients' data were kept confidential, and no patients' identifiers were included in data files handled for the purposes of this study.

Data analysis

The major outcome evaluated was hospital survival for patients admitted or transferred to the ICU during the index admission. Employing Cox proportional hazards model we performed a risk factor analyses for in-hospital survival. Secondly, we evaluated the impact of anti-inflammatory therapy on patient survival.

Summary statistics were computed for the survivors, non-survivors, and treatment groups. Four treatment groups were evaluated: All patients who received GC therapy, GC therapy alone, tocilizumab + GC therapy, tocilizumab alone, and standard treatment alone (no anti-inflammatory therapy). The use of subcutaneous heparin (fractionated or unfractionated), use of convalescent plasma, azithromycin, hydroxychloroquine, antibiotic therapy, and vasopressor use were included as standard therapy. Due to our previous use of intravenous ascorbic acid (IVAA) in sepsis, IVAA use was evaluated as an adjunct treatment modality. We performed both univariate and multivariate analyses. Continuous variables were expressed as median with interquartile ranges, and compared by the Student's *t*-test or the Wilcoxon rank-sum test as appropriate. Multiple comparisons were analyzed with Kruskal Wallis ANOVA or Bonferroni correction when indicated. Categorical values were compared with Pearson's chi-squared test and Fisher's exact test when indicated. Kaplan Meir survival curves with log-rank test analysis and Cox proportional hazards analysis were employed to compare factors associated with survival and to compare treatment groups. Variables that were significant by univariate analysis at $P < 0.05$ were candidates for multivariate analysis. Multivariate Cox proportional hazards with forward variable selection was performed to determine variables independently predictive of survival and for comparing anti-inflammatory therapy groups with standard care.

As there was the possibility of factors influencing the use of corticosteroids, a logistic regression analysis was implemented to create a propensity score for corticosteroid use. A propensity score was generated employing the following factors; age, sex, race, the diagnosis of chronic obstructive pulmonary disease (COPD), need for mechanical ventilation, and PaO_2/FiO_2 ratio on admission. Cox proportional hazards analysis with time to corticosteroid administration as a time-dependent covariate was employed to compare survival among groups. Survival analysis was performed with propensity score adjusted multivariate Cox proportional hazards analysis. Finally, we repeated Cox proportional hazards analysis with both propensity score adjustment and with time to corticosteroid administration as a time-dependent covariate.

RESULTS

Patient characteristics

From March 12, 2020 to June 17, 2020, 261 patients with COVID-19 were admitted to the ICU. There were 94 patients (36%) admitted directly to the ICU and 167 (64%) patients who were initially admitted to non-ICU COVID units then later transferred to ICU. During these four months, hospital mortality for ICU patients was 64% (167 patients). On univariate analysis, there was no significant difference in mortality between those directly admitted to ICU 59 (62%) *vs* transferred to ICU 108 (64%), (P = 0.74, odds ratio 0.92, 95% confidence interval 0.54-1.55). The median time to transfer to ICU was 3 d [interquartile range (IQR) 1-5]. In those patients not initially admitted to ICU, there was no statistically significant difference in time to ICU transfer between survivors and non-survivors median time 2 d (IQR 1-5) *vs* 3 d IQR (1-6) (P = 0.11). There was a statistically significant difference in SOFA scores in patients admitted to the ICU in comparison to those admitted to COVID-19 units [6 (IQR 3-10) *vs* 3.5 (IQR 2-5) P < 0.001]. The median age was 69 years (IQR 61-80), 60% of patients were greater than 65 years and 30% were older than 77, 129 patients (48%), were Caucasian and 158 (60%) were males. The majority of patients (n = 178, 68%) had or developed severe respiratory failure requiring mechanical ventilation, and 39 (15%) required hemodialysis. Of note 167 patients received corticosteroids; either hydrocortisone 100mg every 8 h (n = 12, 7%) or methylprednisolone 40mg every 12 h (n = 155, 92%). A total of 73 patients received GC alone, 94 received both tocilizumab and GC, 28 were on tocilizumab therapy alone, and 66 patients did not receive anti-inflammatory therapy. The dose of tocilizumab employed was 8 mg/kg.

Univariate analysis: Predictors of survival and treatment

Patient characteristics are described in Table 1. Univariate predictors of decreased survival included the need for mechanical ventilation, AKI, Caucasian race, male sex, older age, lower total lymphocyte count, higher neutrophil/lymphocyte ratio, and a greater degree of respiratory failure manifested by a lower PaO_2/FIO_2 ratio. Therapeutic and pharmacologic interventions are described in Table 2. Survival analysis employing univariate Cox proportional hazards analysis revealed patient survival was associated with use all patients receiving GC (GC alone and GC + tocilizumab), GC use alone, less use of vasopressors, and combination therapy with tocilizumab with GC (Table 3). It is pertinent to note that there was no statistically significant difference in survival with the use of anticoagulant doses of heparin, subcutaneous heparin, convalescent plasma, tocilizumab alone, prone ventilation, IVAA, hydroxychloroquine, or azithromycin use. All patients who received remdesivir expired (n = 6, 3%). As anticipated non-survivors demonstrated a higher degree of elevated inflammatory and pro-thrombotic markers interleukin-6 at 48 h, D-Dimer at 24 h and 48 h respectively (Table 4).

Multivariate analysis/Cox proportional hazards analysis

To identify independent predictors of survival, we performed multivariate Cox proportional hazards analysis with stepwise forward variable selection which revealed the following as independent predictors of decreased survival: increased age, male sex, and a requirement for vasopressors. GC use including those patients receiving GC alone and those receiving GC + tocilizumab was associated with survival (Table 5). Kaplan Meier survival analysis curves Kaplan Meier curve for GC treatment (GC alone and GC + tocilizimab) is represented in Figure 1 (GC use, log rank test P < 0.001).

As there was the possibility of factors influencing the use of GC, a logistic regression analysis was implemented to create a propensity score for GC use. A propensity score was generated employing the following factors; age, sex, race, the diagnosis of COPD, need for mechanical ventilation, and PaO_2/FIO_2 ratio on admission (Table 1 and Supplementary Figure 1). In order to confirm that anti-inflammatory therapy influenced survival we next repeated a propensity score adjusted Cox proportional hazards analysis with stepwise forward variable selection including GC alone, tocilizumab + GC, tocilizimab alone, and standard treatment. The model revealed independent predictors of decreased survival remained unchanged, conversely both GC alone and GC + tociluzimab were associated with survival (Table 6). The Kaplan Meier comparing all treatment groups is represented in Figure 2A (log rank test P < 0.001). Separate Kaplan Meier comparing each group and standard care are represented in Figure 2B (GC and standard of care, log rank P = 0.002), and Figure 2C (tocilizumab + GC and standard care, log rank P = 0.016), and Figure 2D (tocilizumab alone and standard care, log rank P = 0.061).

Table 1 Coronavirus disease 2019 patients admitted to intensive care unit characteristics of survivors and non-survivors, *n* (%)

	Non-survivor (*n* = 167)	Survivor (*n* = 94)	*P* value	OR	95%CI
Age	71 (61, 82)	61 (62, 78)	0.011		
Race (Caucasian)	89 (75)	40 (56)	0.007	2.37	1.27-4.40
BMI	29 (23, 34)	28 (24, 32)	0.49		
Sex (male)	75 (70)	83 (53)	0.01	0.49	0.29-0.84
Diabetes	31 (29)	53 (34)	0.3	1.26	0.75-2.2
CHF	13 (12)	21 (14)	0.7	1.1	0.66 – 2.4
CAD	24 (29)	41 (27)	0.41	1.2	0.7-2.2
COPD	38 (23)	23 (30)	0.75	0.9	0.5-1.6
CKD	11 (10)	21 (17)	0.1	1.85	0.87-3.83
HTN	54 (51)	91 (59)	0.16	1.4	0.86-2.3
AKI	87 (52)	30 (32)	0.002	2.3	1.21-2.5
Mechanical ventilation	134 (80)	44 (47)	< 0.001	4.7	2.7-8.3
Hemodialysis	29 (18)	10 (11)	0.13	1.8	0.3-3.9
Neutrophils × 10^9/L	7.3 (4, 10)	7.8 (5.1, 13)	0.97		
Lymphocytes	0.7 (0.5, 1.2)	0.9 (0.6, 1.6)	0.011		
Neutrophil/lymphocyte	10 (6, 18)	7.5 (4, 14)	0.017		
SCr (mg/dL)	1.2 (0.9, 1.9)	1.2 (0.8, 1.8)	0.49		
Plts (× 10^9 /L)	230 (162, 310)	236 (182, 302)	0.27		
Tbili (mg/dL)	0.5 (0.4, 0.8)	0.5 (0.4, 0.8)	0.65		
SOFA admit	5 (3, 9)	4 (2, 6)	0.095		
PaO_2/FIO_2	190 (76, 285)	232 (123, 307)	0.039		
PaO_2	68 (52, 116)	66 (48-112)	0.083		
FIO2	1 (0.45, 1)	1 (0.96, 1)	0.12		

OR: Odds ratio; CI: Confidence interval; CAD: Coronary artery disease; COPD: Chronic obstructive pulmonary disease; CKD: Chronic kidney disease; CHF: Congestive heart failure; AKI: Acute kidney injury; HD: Hemodialysis; tBili: Total bilirubin; Plts: Platelets INR: International normalized ratio. PaO_2 /FiO_2: Partial pressure of oxygen/inspired concentration of oxygen ratio; SOFA: Sequential Organ Failure Assessment; BMI: Body mass index; SCr: Serum creatinine.

In order to adjust for time of GC administration, we employed a propensity score adjusted Cox proportional hazards analysis adjusting GC administration as a time dependent covariate, which revealed independent predictors of decreased survival were: increased age, male sex, and a requirement for vasopressors. GC use including those patients receiving GC alone and those receiving GC + tocilizimab was associated with survival. Conversely, the addition of GC as the time adjusted covariate was associated with a significant decrease in survival and negatively impacted the survival impact of GC treatment suggesting that later initiation of GC is associated with a negative impact on survival (Table 7). The analysis was repeated comparing all treatment groups which revealed the same independent predictors of decreased survival were the following: Increased age, male sex, and a requirement for vasopressors. The groups receiving GC alone and those receiving GC + tocilizumab were associated with survival (Table 8).

Cox proportional hazards analysis adjusted for differences among groups

Among treatment groups, there were significant differences in baseline characteristics observed on univariate analysis (Table 6). In order to adjust for these differences, we repeated the previous Cox proportional hazards analysis model incorporating SOFA score, baseline SCr, FiO2, history of coronary artery disease, and CRP at 24, and all previous variables analyzed on previous Cox models. The propensity score adjusted Cox proportional hazards model with GC as a time dependent covariate demonstrated

Table 2 Pharmacologic and therapeutic interventions in coronavirus disease 2019 intensive care unit patients, *n* (%)

	Non-survivor (*n* = 167)	Survivor (*n* = 94)	*P* value	OR	95%CI
GC (all patients)[1]	99 (59)	68 (72)	0.035	0.55	0.32-0.96
Vasopressors	124 (74)	35 (37)	< 0.001	4.8	2.8-8.4
IV Ascorbic acid	100 (59)	54 (57)	0.7	1.1	0.66-1.84
Hydroxychloroquine	128 (78)	69 (75)	0.57	1.2	0.65-2.1
Azithromycin	65 (40)	25 (26)	0.06	1.69	0.97-2.9
Heparin therapeutic dose	80 (48)	51 (54)	0.32	0.77	0.46-1.3
Heparin prophylaxis dose	58 (35)	32 (34)	0.91	1.03	0.6-1.75
Convalescent plasma	44 (26)	27 (29)	0.68	0.88	0.5-1.56
Remdesivir	6 (3)	0 (0)			
Prone positioning	52 (31)	32 (35)	0.91	1.03	0.6-1.75
Tocilizumab	20 (12)	8 (8.5)	0.55	1.28	0.56-2.9
GC only	44 (26)	29 (30)	0.47	0.8	0.48-1.4
GC + tocilizumab	55 (32)	39 (40)	0.16	0.68	0.4-1.15

[1]Treatment stratified as total patients receiving glucocorticoid (GC) therapy (GC alone and GC + tocilizumab).
GC: Glucocorticoid; OR: Odds ratio; CI: Confidence interval; IV: Intravenous.

Table 3 Univariate Cox proportional hazards survival analysis of pharmacological and therapeutic interventions in coronavirus disease 2019 intensive care unit patients

	B	SE	*P* value	HR	95%CI
GC (all patients)	-0.84	0.16	< 0.001	0.45	0.38-0.61
Vasopressors	0.039	35	0.027	1.4	1.05-2.1
IV ascorbic acid	0.1	0.15	0.49	1.1	0.91-1.5
Hydroxychloroquine	-0.58	0.36	0.1	0.56	0.27-1.14
Azithromycin	0.25	28	0.39	1.3	0.72-2.3
Heparin therapeutic dose	0.15	0.35	0.67	1.16	0.51-2.31
Heparin prophylaxis dose	-0.27	0.3	0.35	0.76	0.48-1.3
Convalescent plasma	0.29	1	0.77	1.3	0.72-9.8
Remdesivir	6 (3)	0			
Prone positioning	0.36	0.52	0.44	1.43	0.51-1.4
Tocilizumab	-0.48	0.27	0.08	0.61	0.36-1.06
GC only	-0.75	0.21	0.001	0.47	0.18-0.41
GC + tocilizumab	-1.3	0.21	<0.001	0.27	0.4-1.15

HR: Hazard ratio; CI: Confidence interval; GC: Glucocorticoids; IV: Intravenous.

that older age, higher SOFA score, and higher baseline SCr were associated with poor outcomes while the combination of tocilizumab and GC was associated with increased survival (Table 7).

DISCUSSION

During the first wave of the pandemic patients requiring admission to the ICU were associated with a mortality of 30%-70%[29-33]. The requirement for mechanical

Table 4 Inflammatory markers in coronavirus disease 2019 survivors and non-survivors

	Non-survivors (*n* = 167)	Survivors (*n* = 94)	*P* value
IL-6 day 1 (pg/mL)	112 (70, 137)	100 (70, 135)	0.34
IL-6 day 2	415 (139, 476)	350 (78, 423)	0.016
D-dimer day 1 (ng/mL)	1125 (647, 2434)	991 (513, 2196)	0.04
D-dimer day 2	849 (604, 1210)	1140 (646, 2263)	0.03
CRP day 1 (mg/L)	117 (89, 159)	113 (96, 149)	0.9
CRP day 2	107 (81, 154)	117 (88, 167)	0.62
Ferritin day 1 (ng/mL)	931 (593, 1367)	960 (609, 1395)	0.51
Ferritin day 2	822 (447, 1432)	1053 (712, 2057)	0.05

IL-6: Interleukin 6, CRP: C-reactive protein.

Table 5 Unadjusted Cox proportional hazards analysis of independent predictors of survival in intensive care unit patients with coronavirus disease 2019

	B	SE	*P* value	HR	95%CI
Age	0.031	0.007	< 0.001	1.032	1.02-1.05
Sex (male)	0.39	0.2	0.046	1.48	1.008-2.2
Vasopressors	0.485	0.2	0.016	1.62	1.095-2.4
GC administration (all patients)[1]	-0.61	0.19	0.002	0.54	0.37-0.79

[1]Treatment stratified as total patients receiving GC therapy (GC alone and GC + tocilizumab).
HR: Hazard ratio; CI: Confidence interval; GC: Glucocorticoids.

Table 6 Propensity score adjusted Cox proportional hazards analysis of independent predictors of survival in intensive care unit patients with coronavirus disease 2019

	B	SE	*P* value	HR	95%CI
Age	0.03	0.007	< 0.001	1.031	1.02-1.05
Sex (male)	0.41	0.2	0.038	1.51	1.022-2.22
Vasopressors	0.47	0.23	0.019	1.6	1.081-2.37
GC + Tocilizumab	-0.78	0.22	0.001	0.46	0.29-0.72
GC only	-0.44	0.22	0.048	0.65	0.42-0.99

SE: Standard error; HR: Hazard ratio; CI: Confidence interval; GC: Glucocorticoids; IV: Intravenous.

ventilation is associated with the highest mortality[30-32,34]. One observational study from Wuhan Du *et al*[30] reported that all 52 patients admitted to the ICU expired during the index hospitalization. In the present study, mortality was consistent with previously reported studies particularly, due to the large percentage of patients requiring mechanical ventilation[30-32,35]. Similarly, we demonstrate that male sex, advancing age, and requirements for vasopressor support were independent predictors of decreased survival[32,36]. Similar to experiences in Wuhan, patients not initially admitted to ICU had significant organ dysfunction with a median SOFA score of 3[30].

The geographical area that the hospitals in the current study services represent one of the largest Medicare populations in the country. Thus overall, the current study represents treatment in an older group of patients and patients requiring mechanical ventilation when compared to the RECOVERY trial and the Northwell COVID-19 treatment consortium[14,37]. The results of the current study demonstrating improved

Table 7 Propensity score adjusted (glucocorticoids as a time-adjusted covariate) Cox proportional hazards analysis of independent predictors of survival in intensive care unit patients with coronavirus disease 2019

	B	SE	*P* value	HR	95%CI
Time adjusted GC	2.5	1.01	0.014	12.9	1.06-87.5
Age	0.03	0.007	< 0.001	1.03	1.01-1.04
Sex (male)	0.4	0.2	0.05	1.5	1-2.17
Vasopressors	0.51	0.2	0.01	1.66	1.12-2.4
GC (all patients)[1]	-2.94	1.01	0.004	0.05	0.007-0.36

[1]Treatment stratified as total patients receiving glucocorticoids (GC) therapy (GC alone and GC + tocilizumab).
SE: Standard error; HR: Hazard ratio; CI: Confidence interval; GC: Glucocorticoids.

Table 8 Propensity score adjusted (glucocorticoids as a time adjusted covariate) Cox proportional hazards analysis of independent predictors of survival in intensive care unit patients with all treatment groups added into the model

	B	SE	*P* value	HR	95%CI
Time adjusted GC	2.5	1.01	0.015	12	1.62-85
Age	0.03	0.007	< 0.001	1.03	1.01-1.04
Sex (male)	0.4	0.2	0.04	1.5	1.01-2.2
Vasopressors	0.5	0.2	0.01	1.66	1.12-2.45
GC + tocilizumab	-3.07	1.02	0.003	0.046	0.006-0.46
GC (only)	-2.77	1.02	0.007	0.06	0.008-0.46

SE: Standard error; HR: Hazard ratio; CI: Confidence interval; GC: Glucocorticoids.

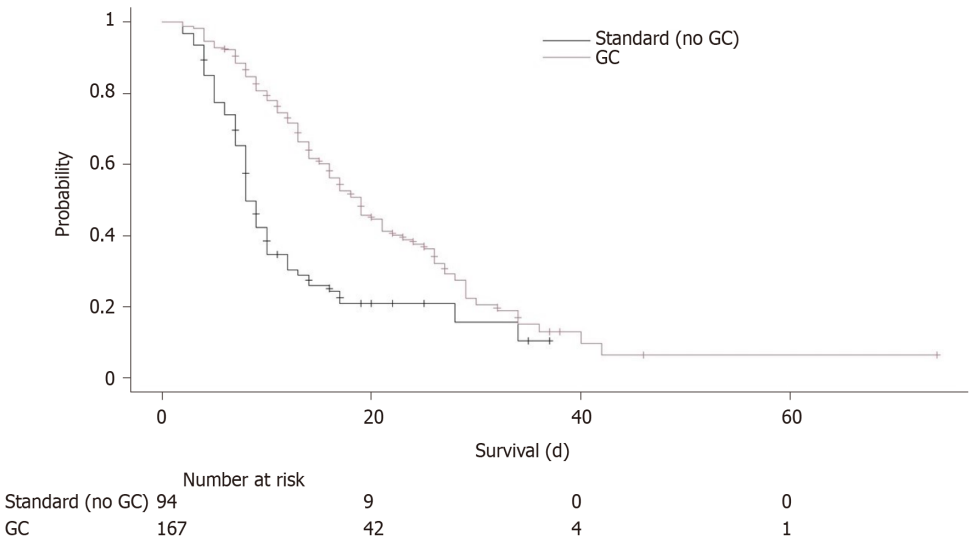

Figure 1 Kaplan Meier survival curve demonstrating increased survival in all patients who received glucocorticoid (red line) *vs* no glucocorticoid therapy (black line) log-rank test *P* < 0.001.

survival in patients receiving anti-inflammatory should be viewed with this context in mind.

A dysregulated immune response resulting in a hyper-inflammatory state is a hallmark of COVID-19 patients who develop severe progressive respiratory failure and multi-organ dysfunction[38]. A small percentage of these patients have clinical characteristics and laboratory parameters similar to macrophage activation syndrome or cytokine storm seen in H1N1 influenza and CAR-T therapy[39-42]. Although many

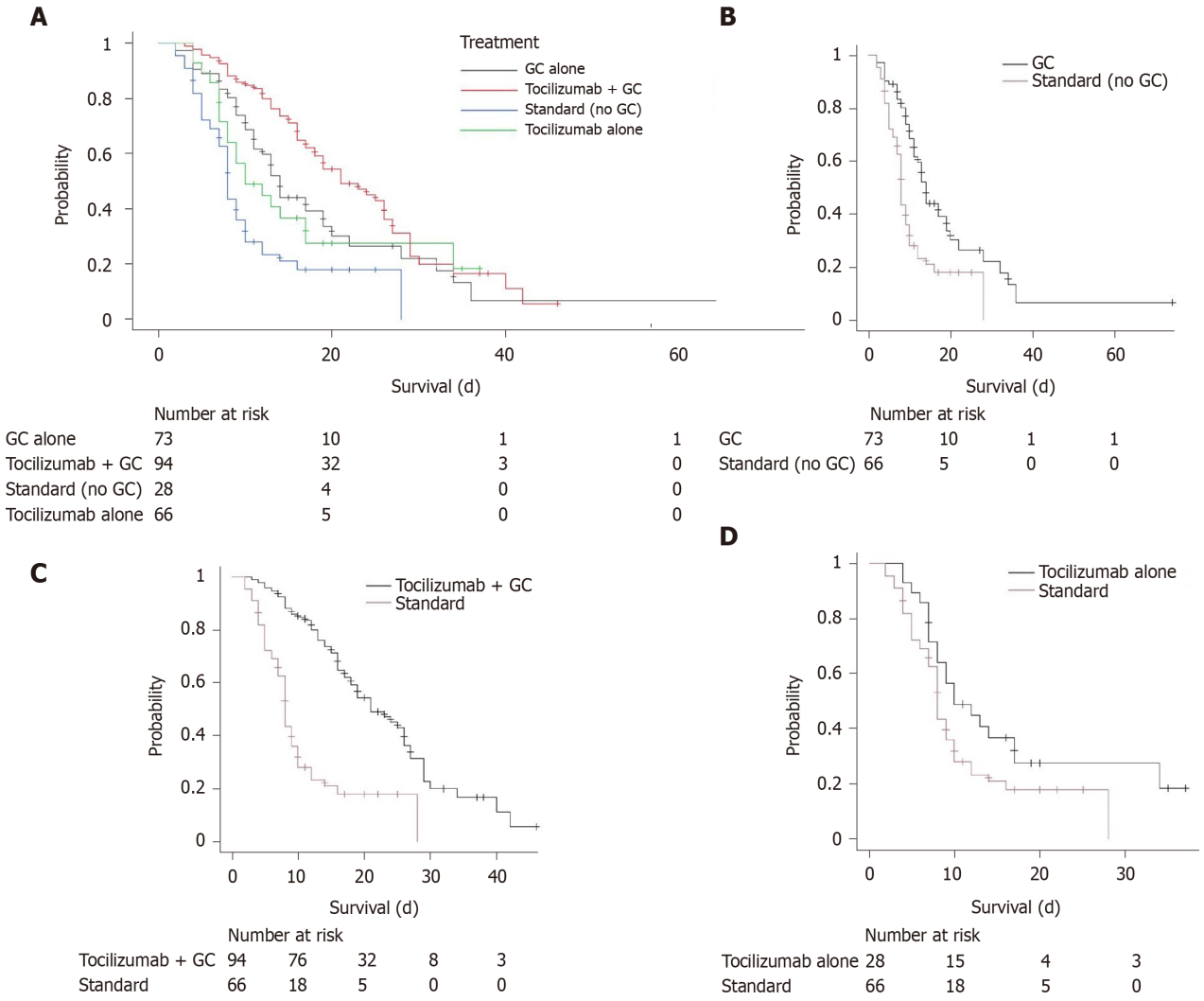

Figure 2 Kaplan Meier survival curve. A: Kaplan Meier survival curve demonstrating increased survival differences in groups receiving tocilizimab + glucocorticoid (GC) (red line), GC alone (black line), tocilizumab alone (green line), and standard treatment (blue line), log rank test with Bonferroni adjustment, $P < 0.001$; B: Kaplan Meier survival curve comparing groups GC alone (black line), and standard treatment (red line) log rank test, $P < 0.001$; C: Kaplan Meier survival curve comparing groups tocilizumab + GC (black line), and standard treatment (red line) log rank test, $P = 0.016$; D: Kaplan Meier survival curve comparing groups tocilizumab (black line), and standard treatment (red line) log rank test, $P = 0.062$.

pro-inflammatory cytokines are elevated in patients with severe COVID -19 infection, there is mounting evidence that increased pro-inflammatory cytokine signatures of IL-6 and TNF-α correlate with severity of disease and increased mortality[38,43,44]. Thus, from therapeutic standpoint therapies that inhibit the NFK-β pathway and IL-6 make GC and tocilizumab prime therapeutic candidates[37-38].

During the first wave of the pandemic, the use of anti-inflammatory therapy may have been predicted by understanding the pathophysiology of cytokine storms observed in CAR-T and in previous influenza viruses, experience in ARDS, and by some who believed the evidence supported the use of GC in viral pneumonia[22,45-47]. Long *et al*[48] reported improvement in mortality outcomes in 5327 patients with SARS associated with MERS in those patients receiving GC therapy. Likewise, Li *et al*[49] reported improved mortality outcomes in patients hospitalized with A(H1N1)pdm09 influenza[46,48-50]. In March 2020, Wu reported an observational study of 84 patients revealing reduced mortality risk in patients with ARDS risk receiving methylprednisone[50].

Prior to the RECOVERY trial, the use of GC in the treatment of severe COVID-19 was considered controversial and potentially harmful as treatment possibly could increase and prolong viral shedding. To some degree treatment with GC is still not without controversy[16,51]. Towards the end of the third wave, there has been increasing evidence from randomized controlled trials and observational studies that GC therapy improves survival in severe COVID-19, and the use of GC in low to moderate dosing is not associated with increased viral shedding[14,15,51,52]. To date,

the use of anti-cytokine therapy mainly with anti-IL-6 treatment with tocilizumab has yielded mixed results[53-55].

In many infections, it is not the pathogen that determines the virulence of the disease. Instead, it is the host response to the pathogen that causes tissue injury, delayed healing, morbidity, and mortality. COVID-19 associated respiratory failure is a cehost response hyper-inflammatory pulmonary disease driven by macrophages and hyper-cytokinemia[54-56]. Of note, most patients with SARS-CoV-2 infection are mild or completely asymptomatic, with only a minority progressing to severe illness[54]. In the setting of mild or asymptomatic disease, there is an appropriate release of antiviral interferons, clearance of viral debris by phagocytosis, and a controlled innate immune response followed by the development of adaptive immunity[54,56,57]. However, there is an impaired release of interferons and an abnormal innate immune response associated with excessive hyper-inflammatory response in the small subset of patients progressing to severe disease[57]. Although SARS-CoV-2 viral cytopathic effect on the epithelial cells of the respiratory tract has been demonstrated, investigators have found it challenging to retrieve live virus during the severe symptomatic pulmonary phase of the disease despite clinical evidence of tissue injury and damage[58]. The positive response of anti-inflammatory and immunomodulatory agents in severe SARS-CoV-2 infection underscores the dysregulated hyper-inflammatory host response responsible for the tissue damage and virulence of severe COVID-19.

Although in the present study elevated body mass index did not significantly correlate with mortality, hyper-nutrition (sarcopenic obesity) is a known risk factor for developing severe COVID-19 disease and mortality[59]. Due to increased expression of the angiotensin converting enzyme-2 receptor, adipose tissue is a target for SARS-CoV-2 infection, adipose tissue function as an endocrine organ which results in a pro-inflammatory state, activation of NOD-, LRR-, and pyrin domain-containing protein 3 inflammasome and release of pro-inflammatory cytokines[60-63]. In addition, increase adipose tissue increases circulating TNF-α and IL-6[61]. Furthermore, obesity is associated with CD-4 T-cell exhaustion and decreases in anti-inflammatory cytokines IL-10 and IL-4[61,64,65]. Thus hyper-nutrition obesity sarcopenic patients are at higher risk for acquiring infection and developing the inflammatory immune dysregulation observed in severe COVID-19 disease[61,65].

Unfortunately, the current study did not investigate the presence gastrointestinal (GI) manifestation of severe COVID-19 disease. Further studies are needed to explore the possible organ crosstalk between the pulmonary and GI systems as the GI tract is both a driver of inflammation and a potential infectious source[66].

In the current study, we demonstrated the survival benefit of anti-inflammatory therapy employing several Cox proportional hazard models. Firstly, univariate analysis of therapy revealed survival benefit in all patients receiving GC treatment and tocilizumab + GC treatment while tocilizumab alone offered no survival benefit. Unadjusted multivariate analysis, propensity score adjusted Cox proportional hazard with and without GC use as a time-adjusted covariate supported survival benefits observed in the univariate analysis. Cox proportional hazards with GC therapy as a time dependent covariate suggest that earlier treatment with GC offers a greater survival benefit. After adjusting for differences among patient groups, combination therapy with tocilizumab + GC remained associated with increased patient survival. Overall combination therapy with tociluzimab + GC offered the greatest survival benefit.

The strengths of the current study are it represents a real world scenario in the treatment of critically ill patients in a predominantly older population with COVID-19 during the first wave of the pandemic when there was a paucity of randomized controlled evidence guiding therapy. Study limitations include the retrospective nature of the study and the difficulty in adjusting for confounding due to multiple interventions involved.

CONCLUSION

Anti-inflammatory therapy with GC and combination treatment with tocilizumab and GC improve survival in critically ill patients with COVID-19. Dual inhibition of the NFK-β therapy with GC and inhibition of the Il-6 pathway with tocilizumab may offer greater survival benefits. It is pertinent to note that monotherapy with tocilizumab alone was not associated with an increase in survival. Further prospective studies investigating combination anti-inflammatory therapy and timing of initiation of therapy are needed.

ARTICLE HIGHLIGHTS

Research background

Anti-inflammatory therapies have been the focus of treatment for severe hospitalized coronavirus disease 2019 (COVID-19) patients. Mixed literature has led to multiple approaches to providing these immune-modulating agents to calm the host response which has been shown to cause severe illness. Our study provides a retrospective evaluation of treatment provided to ICU-admitted COVID-19 patients and their outcomes.

Research motivation

Corticosteroids have clearly been the mainstay of treatment for hypoxic COVID-19 patients, but there has been debate on the best approach for additional anti-inflammatory therapies. Studies surrounding tocilizumab have previously shown mixed results complicated by a changing treatment regimen as we learned more about the disease process.

Research objectives

The objective of this evaluation was to evaluate treatment provided to severe COVID-19 patients early in the pandemic at our institution and provide additional guidance on any regimens which were associated with improvement in patient outcomes. What was clear after our assessment was that anti-inflammatory therapies using corticosteroids, potentially in combination with tocilizumab, could provide the best outcomes for our patients.

Research methods

Two hundred and sixty-one patients admitted to two community hospital intensive care units for severe COVID-19 were retrospectively analyzed for risk factors for mortality using propensity matched scoring.

Research results

Patient survival was associated with corticosteroid use, with or without tocilizumab. Timing of administration of corticosteroids was an important factor which determined patient outcomes with delays leading to decreased survival. No differences were found with use of anticoagulation, convalescent plasma, tocilizumab monotherapy, prone ventilation, hydroxychloroquine, azithromycin, or intravenous ascorbic acid use.

Research conclusions

Anti-inflammatory therapy with corticosteroids with or without tocilizumab was associated with the best outcomes in our cohort of severe COVID-19 patients.

Research perspectives

More trials are needed based on the appropriate dose, timing, and duration of corticosteroids in COVID-19. The benefit of tocilizumab and corticosteroids as combination treatment also needs to be explored further in randomized trials.

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