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MAJOR ARTICLE

Real-Life Effectiveness and Safety of Baricitinib as Adjunctive to Standard-of-Care Treatment in Hospitalized Patients With Severe Coronavirus Disease 2019

Nikolaos Tziolos,[1,a] Emmanouil Karofylakis,[1,a] Ioannis Grigoropoulos,[2,a] Pinelopi Kazakou,[1] Emmanouil Koullias,[2] Athina Savva,[1] Hariklia Kranidioti,[2] Aimilia Pelekanou,[1] Anna Boulouta,[1] Maria Pirounaki,[2] Sotirios Tsiodras,[1] Georgios Georgiopoulos,[2] Dimitrios T. Boumpas,[1] Dimitra Kavatha,[1,a] Konstantinos Thomas,[1,a] Dimitrios Vassilopoulos,[2,a] and Anastasia Antoniadou[1,a]

[1]4th Department of Internal Medicine, National and Kapodistrian University of Athens School of Medicine, Attikon University General Hospital, Chaidari, Greece; [2]2nd Department of Medicine and Laboratory, National and Kapodistrian University of Athens School of Medicine, Hippokration General Hospital, Athens, Greece

Background. Therapeutic options for hospitalized patients with severe coronavirus disease 2019 (sCOVID-19) are limited. Preliminary data have shown promising results with baricitinib, but real-life experience is lacking. We assessed the safety and effectiveness of add-on baricitinib to standard-of-care (SOC) including dexamethasone in hospitalized patients with sCOVID-19.

Methods. This study is a 2-center, observational, retrospective cohort study of patients with sCOVID-19, comparing outcomes and serious events between patients treated with SOC versus those treated with SOC and baricitinib combination.

Results. We included 369 patients with sCOVID-19 (males 66.1%; mean age 65.2 years; median symptom duration 6 days). The SOC was administered in 47.7% and combination in 52.3%. Patients treated with the combination reached the composite outcome (intensive care unit [ICU] admission or death) less frequently compared with SOC (22.3% vs 36.9%, $P = .002$). Mortality rate was lower with the combination in the total cohort (14.7% vs 26.6%, $P = .005$), and ICU admission was lower in patients with severe acute respiratory distress syndrome (29.7% vs 44.8%, $P = .03$). By multivariable analysis, age (odds ratio [OR] = 1.82, 95% confidence interval [CI] = 1.36–2.44, per 10-year increase), partial pressure of oxygen/fraction of inspired oxygen ratio (OR = 0.60, 95% CI = .52–0.68, per 10 units increase), and use of high-flow nasal cannula (OR = 0.34; 95% CI, .16–0.74) were associated with the composite outcome, whereas baricitinib use was marginally not associated with the composite outcome (OR = 0.52; 95% CI, .26–1.03). However, baricitinib use was found to be significant after inverse-probability weighted regression (OR = 0.93; 95% CI, .87–0.99). No difference in serious events was noted between treatment groups.

Conclusions. In real-life settings, addition of baricitinib to SOC in patients hospitalized with sCOVID-19 is associated with decreased mortality without concerning safety signals.

Keywords. baricitinib; COVID-19; dexamethasone; ICU admission; respiratory failure.

In late 2019, a novel coronavirus was identified as the cause of cluster pneumonia cases in China. The "culprit" virus was identified as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease 2019 (COVID-19) has subsequently spread worldwide. Management of hospitalized patients has been rapidly evolving, with the World Health Organization (WHO) and the National Institutes of Health issuing interim guidance [1, 2]. Currently, the main constituents of in-hospital treatment are dexamethasone, remdesivir, as well as Janus kinase inhibitors ([JAKi] baricitinib, tofacitinib) and interleukin (IL)-6 pathway inhibitors (tocilizumab, sarilumab) as add-on therapy for patients with increasing oxygen needs.

A state of hyperinflammation was observed in critical cases, with characteristically elevated inflammatory markers and proinflammatory cytokines [3]. Based on these observations, many experts contemplated the use of immunosuppressive agents such as glucocorticoids for patients with severe disease [4]. Targeting the dysregulated host immune response, several other immunomodulatory agents have been tested in patients with COVID-19 [5].

The unmet need for effective treatment of severe COVID-19 (sCOVID-19) has been illustrated in the pivotal ACTT-1 [6] and RECOVERY [7] trials that formed the basis of current standard-of-care (SOC) treatment. In the former study, use of

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[a]N. T., E. K., I. G., D. K., K. T., D. V., and A. A. contributed equally to the manuscript as first and last authors, respectively.

Correspondence: Konstantinos Thomas, MD, Consultant of Internal Medicine – Infectious Diseases, 4th Department of Internal Medicine, National and Kapodistrian University of Athens School of Medicine, Attikon University General Hospital, 1 Rimini Str., 124 62 Chaidari, Greece (costas_thomas@yahoo.com).

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remdesivir did not reduce the time to recovery in patients who received high-flow oxygen or noninvasive mechanical ventilation, whereas in the latter, dexamethasone use led to only a small decrease of 4.2% in age-adjusted 28-day mortality in patients needing oxygen supplementation.

Using artificial intelligence, it was presumed that baricitinib, a JAKi approved for the treatment of rheumatoid arthritis and atopic dermatitis, had antiviral activity by interfering with viral cell entry [8, 9]. In addition, this JAKi has clinically proven immunomodulatory properties by inhibiting the signaling of various pro-inflammatory cytokines such as IL-2, IL-4, IL-6, etc, interferons ([IFN]-α, -β, and -λ), and growth factors (granulocyte-macrophage colony-stimulating factor [CSF] and granulocyte-CSF) [10, 11].

Data on the efficacy and safety of baricitinib as add-on therapy to current SOC regimens are sparse. In the randomized controlled trial (RCT) ACTT-2 of baricitinib use in COVID-19, glucocorticoids were used only for standard indications; therefore, few patients received this drug combination [12]. In ACTT-2, baricitinib and remdesivir combination was superior to remdesivir alone in terms of recovery time, especially among patients on high-flow oxygen or noninvasive ventilation. Recently published data suggest a survival benefit with the use of baricitinib for hospitalized patients with COVID-19 [13]. In this randomized, placebo-controlled trial of over 1500 hospitalized patients, adding baricitinib to SOC reduced 28- and 60-day mortality. Patients on high-flow oxygen or noninvasive ventilation exhibited a similar reduced mortality rate with the use of baricitinib (17% vs 29%, hazard ratio [HR] = 0.52). Eighty percent of the study population received concomitant glucocorticoids, primarily dexamethasone, significantly more than the earlier randomized study that showed a potential benefit with baricitinib [12]. A more recent observational study with propensity score-matched controls showed a lower rate of death or mechanical ventilation associated with baricitinib use, with 86% of patients (71 of 83) receiving concomitant glucocorticoids [14].

We studied the effectiveness and safety of combined dexamethasone and baricitinib treatment in a real-life cohort of patients with severe disease, all of them requiring high-flow oxygen at the time of baricitinib initiation.

PATIENTS AND METHODS

This is a retrospective cohort study conducted in 2 tertiary academic referral centers for COVID-19 in Metropolitan Athens, Greece, to assess the role of baricitinib as add-on therapy to SOC regimens in hospitalized patients with sCOVID-19. Baricitinib was included as treatment option in the National COVID-19 guidelines and was available through the off-label procedure of the National Organization for Health Care Services.

Inclusion criteria were age ≥18 years, administration of dexamethasone (with or without baricitinib), and severe disease, defined as a score of 6 in the National Institute of Allergy and Infectious Diseases ordinal severity scale of 1–8 (need for high-flow oxygen: venturi mask >15 liters/minute, non-rebreather bag, high-flow nasal cannula [HFNC]) [6]. Patients receiving other immunomodulatory therapies or mechanically ventilated patients at admission were excluded. Patients were recruited from September 2020 until March 2021, with those receiving baricitinib enrolled consecutively between February and March 2021. The study was approved by the hospitals' Ethics Committee.

The SOC regimen was defined as dexamethasone (6 mg/day positive or intravenous), remdesivir (200 mg/day on day 1 and 100 mg/day for subsequent days) in patients presenting before day 10 of symptoms, unless contraindicated (glomerular filtration rate <30 mL/min per 1.73 m^2 or aminotransferases >3× upper normal limit) and low-molecular-weight heparin (LMWH) as thromboprophylaxis. The intermediate dose of LMWH was selectively used, according to National COVID-19 guidelines where it is recommended for patients in the intensive care unit (ICU) or critically ill patients, with high values of inflammation biomarkers such as fibrinogen, D-dimers, or C-reactive protein (CRP) and with low bleeding risk (platelets >25 000/mm^3, normal international normalized ratio, and activated partial thromboplastin time). Therapeutic anticoagulation was given only in proven or highly suspected thrombosis or pulmonary embolism. Antimicrobials were used at the treating physicians' discretion. Baricitinib was administered orally according to its approved dose scheme (4 mg/day) for 14 days or until discharge, if earlier.

A comprehensive documentation of patients' demographics, comorbidities, inflammatory markers, duration of high-flow oxygen therapy, and adverse events was conducted. Severity of respiratory failure was assessed by the minimal partial pressure of oxygen/fraction of inspired oxygen ratio (PaO_2/FiO_2) ratio during hospitalization in the ward. Studied outcomes included a composite outcome of ICU admission or death from any cause (whichever occurred first), death from any cause, ICU admission, and duration of high-flow oxygen therapy in patients that clinically improved. It must be also noted that patients were admitted to the ICU only after intubation. Clinical improvement was defined as transition from an ordinal scale of 6 to 5.

Statistical analyses were performed with SPSS (IBM SPSS Statistics for Windows, v. 25.0; IBM Corp, Armonk, NY), Stata 13.1 (StataCorp), and OpenEpi. Dichotomous variables are shown as percentages and continuous variables are shown as mean (standard deviation) for normal and median (interquartile range) for nonparametric distributions, respectively. The χ^2 test was applied for comparison of dichotomous variables, and Mann-Whitney or *t* test was applied for continuous variables. The threshold of statistical significance was set as $P < .05$ for all comparisons.

We further performed univariable and multivariable logistic regression to identify associates with the composite outcome. We also performed multivariable linear regression analysis to assess the correlation of various factors with the duration of high-flow oxygen therapy (ordinal severity scale score = 6). Age and sex (for the logistic regression) and variables with $P < .1$ in univariable analysis were included in the multivariable model, and those with $P < .05$ were retained until the final stage of the regression models. Variables with a very small number of positive cases (≤5) and similar incidence of the outcome between cases and controls (ie, end-stage renal disease [ESRD], inflammatory diseases) were not considered in the logistic regression analysis to avoid empty cells into respective 2 × 2 contingency tables.

To overcome the nonrandomized design of the study comparing the efficacy of baricitinib and to minimize confounding by indication bias in baricitinib use, we applied a doubly robust inverse probability weighted regression (IPWR) analysis: at first, we computed inverse-probability weights from multivariable logistic regression model on treatment status (therapy with baricitinib or not) (treatment model). We subsequently applied the estimated inverse-probability weights to regress the composite outcome for each treatment level (baricitinib yes or no) and obtained the treatment-specific predicted outcomes for each subject. Covariates used in the treatment model and the outcome model were prespecified. This analysis produces consistent estimates because the treatment is assumed to be independent of the potential outcomes after conditioning on the "covariates". The treatment-independent variables were chosen and included in the model according to the statistically significant differences in biologically significant factors (age) and other treatment or supportive measures between SOC and combination treatment (cardiovascular disease [CVD], use of high-flow nasal cannula, remdesivir).

Free-of-composite outcome survival was evaluated with Kaplan-Meier analysis, and log-rank test was implemented to compare survival among subgroups. Patients were censored at the time of admission in the ICU or at the time of death before ICU admission or at discharge or transfer to a rehabilitation unit.

Incidence of serious events of special interest are presented per 1000 patient-days. We included only serious events occurring at least 1 day after treatment initiation.

Patient Consent Statement

The design of the work has been approved by Attikon University Hospital Ethics Committee (ID: 487/3-9-2020).

RESULTS

Patients' Characteristics at Admission

Three hundred sixty-nine hospitalized patients with sCOVID-19 (ordinal severity scale = 6) were included in the study (66.1% males, mean age 65.2 years). The SOC was administered in 176 (47.7%) and combination with baricitinib in 193 (52.3%). Patients' demographics, comorbidities, and mode of oxygenation are shown in Table 1.

Comparing patients treated with SOC versus SOC plus baricitinib, there were no differences in symptom duration, gender, and severity of respiratory failure expressed as mean minimum PaO_2/FiO_2 ratio. Patients on the standard treatment arm were more likely to suffer from hypertension, CVD and heart failure, ESRD, and active neoplastic or inflammatory disease, whereas those treated with the combination scheme were younger (61.6 ± 12.7 vs 69.1 ± 13.5 years, $P < .001$), received remdesivir more often (83.9% vs 68.8%, P .001), intermediate dose LMWH (45.8% vs 31.8%, P .009), or oxygen by HFNC (39.1% vs 15.3%, $P < .001$) (Table 1).

Outcomes

Free-of-composite outcome in the total cohort was 72% and 54.5% of patients at 14 and 28 days, respectively. During hospitalization, 75 patients (20.3%) were admitted to the ICU and 72 (20.4%) died, whereas 108 (29.3%) reached the composite outcome. Among critically ill patients with severe acute respiratory distress syndrome (ARDS) ($PaO_2/FiO_2 < 100$, n = 188) 50% reached the composite outcome. Clinical improvement was recorded in 264 patients (71%) after a median time of 6 (4–9) days. There was no significant difference in time to clinical improvement with the combination scheme (5 [3–9] vs 6 [4–10] days, $P = .59$).

Overall mortality rate was significantly lower in patients treated with the combination regimen (14.7% vs 26.6%, $P = .005$). Regarding the composite outcome, combination was superior to SOC (22.3% vs 36.9%, $P = .002$), whereas the free-of-composite outcome survival for SOC versus combination was 65.2% versus 84.7% at 14 days and 43.9% versus 63.1% at 28 days (log-rank = 0.002). In subanalysis according to ARDS severity (PaO_2/FiO_2 < or >100), the difference in mortality and the composite outcome was statistically significant in favor of the combination group for both subgroups. Risk of ICU admission was lower only in patients with PaO_2/FiO_2 <100 with the combination scheme (29.7% vs 44.8%, $P = .03$) (Table 2).

Predictors of Intensive Care Unit Admission or Death

By univariable analysis, patients reaching the composite outcome were older, had higher CRP and ferritin levels, lower PaO_2/FiO_2 ratio, were more likely to have a history of CVD, hypertension, and ESRD, and were less likely to have been treated with remdesivir, baricitinib, or receiving oxygen by HFNC (Supplement Table 1).

By multivariable analysis, age was independently associated with higher risk for composite outcome (odds ratio [OR] = 1.82,

Table 1. Patients' Characteristics According to Treatment Type

Variable	Total	SOC	SOC + Baricitinib	P^a
n	369	176	193	
Age, years (SD)	65.2 (13.6)	69.1 (13.5)	61.6 (12.7)	**<.001**
Age >65 years, n (%)	189 (51.2)	106 (60.2)	83 (43)	**.001**
Symptoms duration, days	6 (4)	5 (4)	7 (5)	.03
Minimum PaO_2/FiO_2 ratio (SD)	109 (51)	110 (54)	107 (48)	.65
Sex, male, n (%)	244 (66.1)	121 (68.8)	123 (63.7)	.31
CRP (mg/L)	105 (77)	109 (74)	100 (79)	.28
Ferritin, (ng/mL)	1339 (2505)	1579 (3384)	1124 (1253)	.09
BMI >30, n (%)	75 (20.3)	37 (21)	38 (19.7)	.75
Diabetes, n (%)	93 (25.2)	50 (28.4)	43 (22.3)	.17
Hypertension, n (%)	170 (46.1)	92 (52.3)	78 (40.4)	**.02**
Dyslipidemia, n (%)	112 (30.4)	60 (34.1)	52 (26.9)	.13
COPD/asthma, n (%)	33 (8.9)	21 (11.9)	12 (6.2)	.05
CVD/heart failure, n (%)	53 (14.4)	34 (19.3)	19 (9.8)	**.01**
ESRD, n (%)	12 (3.3)	10 (5.7)	2 (1)	**.01**
Current cancer, n (%)	18 (4.9)	13 (7.4)	5 (2.6)	**.03**
Inflammatory disease, n (%)	12 (3.3)	2 (1.1)	10 (5.2)	**.03**
CCI, median (IQR)	3 (1–4)	4 (2–6)	2 (1–3)	**.001**
Remdesivir, n (%)	283 (76.7)	121 (68.8)	162 (83.9)	**.001**
LMWH				**.009**
No	3 (0.8)	3 (1.7)	0 (0)	
Prophylactic	166 (45.1)	84 (47.7)	82 (42.7)	
Intermediate	144 (39.1)	56 (31.8)	88 (45.8)	
Therapeutic	55 (14.9)	33 (18.8)	22 (11.5%)	
Mode of Oxygenation				**<.001**
MV	132 (35.9)	77 (43.8)	55 (28.6)	
HFNC	102 (27.7)	27 (15.3)	75 (39.1)	
NRB	134 (36.4)	72 (40.9)	62 (32.3)	

Abbreviations: BMI, body-mass index; CCI, Charlson comorbidity index; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CVD, cardiovascular disease; ESRD, end-stage renal disease; FiO_2, fraction of inspired oxygen; HFNC, high-flow nasal cannula; IQR, interquartile range; LMWH, low-molecular-weight heparin; MV, Venturi mask; NRB, non-rebreathing bag; PaO_2, partial pressure of oxygen; SD, standard deviation; SOC, standard-of-care.

[a]Statistically significant differences are presented in bold.

95% confidence interval [CI] = 1.36–2.44, per 10-year increase), PaO_2/FiO_2 ratio (OR = 0.60, 95% CI = 0.52–0.68, per 10 units increase) and use of HFNC (OR = 0.34; 95% CI, 0.16–0.74) were independently associated with decreased risk, whereas the use of baricitinib (OR = 0.52, 95% CI, 0.26–1.03) was not associated with decreased risk. However, after doubly robust IPWR, baricitinib was associated with lower risk for the composite outcome (OR = 0.93; 95% CI, 0.87–0.99) (Table 3, Figure 1).

When we analyzed mortality separately, older age, lower PaO_2/FiO_2 ratio, and the use of HFNC but not remdesivir or baricitinib were associated with reduced mortality (data not shown).

Table 2. Patients' Outcomes According to Treatment Type

Variable	Total	SOC	SOC + Baricitinib	P^a
Time on high-flow oxygen, days (median, IQR)[b]	6 (5)	5 (6)	6 (6)	.59
ICU admission	75 (20.3%)	42 (23.9%)	11 (16.4%)	.21
PaO_2/FiO_2 <100	69 (36.7%)	39 (44.8%)	30 (29.7%)	**.03**
PaO_2/FiO_2 >100	3 (1.7%)	3 (3.4%)	0 (0%)	.24
Death	72 (20.4%)	45 (26.6%)	27 (14.7%)	**.005**
PaO_2/FiO_2 <100	62 (35.6%)	36 (45%)	26 (27.7%)	**.017**
PaO_2/FiO_2 >100	10 (5.7%)	9 (10.1%)	1 (1.1%)	**.01**
ICU or death composite	108 (29.3%)	65 (36.9%)	43 (22.3%)	**.002**
PaO_2/FiO_2 <100	94 (50%)	55 (63.2%)	39 (38.6%)	**.001**
PaO_2/FiO_2 >100	11 (6.3%)	10 (11.2%)	1 (1.1%)	**.006**

Abbreviations: FiO_2, fraction of inspired oxygen; ICU, intensive care unit; IQR, interquartile range; PaO_2, partial pressure of oxygen; SOC, standard of care.

[a]Statistically significant differences are presented in bold.

[b]In n = 264 that achieved reduction in ordinal scale from 6 to 5.

Table 3. Multivariate Logistic Regression Analysis of Factors Associated With Composite Outcome (ICU Admission or Death)

	Multivariate	
Variable	OR (95% CI)	*P*[a]
Male sex	1.55 (0.76–3.17)	.23
Age (per 10 years)	1.82 (1.36–2.44)	**<.001**
CRP (per 100 mg/L)	1.22 (0.83–1.79)	.32
PaO_2/FiO_2 ratio (per 10 units)	0.60 (0.52–0.68)	**<.001**
CVD/heart failure	1.99 (0.77–5.15)	.16
HFNC	0.34 (0.16–0.74)	**.006**
Remdesivir	0.68 (0.32–1.44)	.31
Baricitinib	0.52 (0.26–1.03)	.06
Baricitinib (IPWR)[b]	0.93 (0.87–0.99)	**.03**

Abbreviations: CI, confidence interval; CRP, C-reactive protein; CVD, cardiovascular disease; FiO_2, fraction of inspired oxygen; HFNC, high-flow nasal cannula; ICU, intensive care unit; IPWR, inverse probability weighted regression; PaO_2, partial pressure of oxygen; OR, odds ratio.

[a]Statistically significant differences are presented in bold.

[b]Doubly robust IPWR with the composite outcome as outcome-dependent and baricitinib use as treatment-dependent variable (separate model from logistic regression analysis). Treatment-independent variables included age at admission, HFNC, remdesivir, and prophylactic versus intermediate/therapeutic low-molecular weight heparin.

Time to Improvement

Time to clinical improvement (transition from ordinal scale score 6 to 5) was longer for patients with diabetes (1.7 days) and for patients developing bacterial infection (5.6 days) and decreased by 2.6 days for every 50 units of minimum PaO_2/FiO_2. Baricitinib was not associated with shorter time to improvement (Supplement Table 2).

Serious Events

Patients on SOC and combination regimen contributed 2573 and 2951 patient-days of follow-up, respectively. The incidence rates for bacterial infection, drug-induced liver injury, acute coronary syndrome, or acute kidney injury were similar between the 2 treatment groups. The incidence rate for venous thromboembolism (VTE), although numerically higher in the baricitinib group, did not differ between the 2 treatment groups (Supplement Table 3).

DISCUSSION

The results of this real-life study demonstrate that baricitinib addition to SOC regimen in patients with sCOVID-19 confers a survival benefit. The mortality rate (14.7% vs 26.6%) as well as the composite outcome of ICU admission or death (22.3% vs 36.9%) were significantly lower in the combination group, both for patients with the most severe (PaO_2/FiO_2 <100) as well as those with less severe disease. Lower incidence of ICU admission was noted only in those with PaO_2/FiO_2 <100.

Our target population represents the niche in the COVID-19 spectrum, where dysregulated host immune responses may lead to grave outcomes. Viral replication in the earlier stages of the disease has been targeted with remdesivir, a nucleotide analog initially developed for hepatitis C and investigated for Ebola virus disease. In vitro activity of this drug against SARS-CoV-2 was established early in the course of the pandemic [15]. Published data from ACTT-1, a randomized placebo-controlled trial, suggested reduced time to recovery among patients on low-flow oxygen [6], especially if presenting early after symptoms initiation. On the contrary, no benefit was shown in those needing high-flow oxygen or noninvasive mechanical ventilation. Despite the possible clinical benefit of remdesivir, discrepant results have been published. The WHO-sponsored SOLIDARITY trial was stopped early because no difference in 28-day mortality among patients receiving open-label remdesivir was observed [16]. The probable lack of efficacy of this direct antiviral treatment in patients with severe disease highlights the importance of therapeutic approaches with immunomodulatory agents.

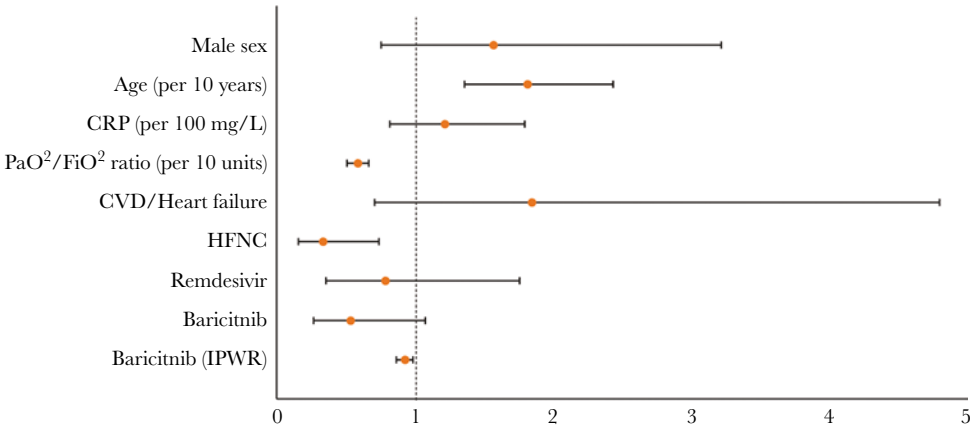

Figure 1. Forest plot of multivariate logistic regression analysis of factors associated with the composite outcome (intensive care unit admission or death). CRP, C-reactive protein; PaO2, partial pressure of oxygen; FiO2, fraction of inspired oxygen; CVD, cardiovascular disease; HFNC, high-flow nasal cannula; IPWR, inverse probability weighted regression.

Despite the widespread use of dexamethasone for patients on supplementary oxygen or ventilatory support, its efficacy for those in need of high-flow oxygenation, but not mechanically ventilated, remains uncertain. The bulk of evidence supporting the use of glucocorticoids in hospitalized adults comes from an RCT conducted in United Kingdom that showed a reduction in 28-day mortality in those receiving dexamethasone compared with usual care [7]. Specifically, an overall 17% relative reduction in mortality was observed, with patients on invasive mechanical ventilation or extracorporeal membrane oxygenation at baseline being benefited the most, showing a 36% relative reduction, compared with 18% in patients on noninvasive supplemental oxygen. Despite these efficacy data and an absolute mortality benefit of 2.9% (23.3% vs 26.2%) in the noninvasive oxygen therapy group of the RECOVERY trial, the fact that approximately 1 of 4 patients of this cohort died signals that there is still room for improvement.

In this study, we evaluated the potential association of patient characteristics, disease features, and treatment type with the prognosis of sCOVID-19. Apart from well established risk factors, such as the age [17] and the severity of respiratory failure, we showed that the use of baricitinib and HFNC as add-on to SOC were associated with reduced risk for ICU admission or death.

Using IPWR analysis, we found that the addition of baricitinib to the SOC was associated with a 7% decrease in the composite outcome. Although this association seems modest, it has to be noted that it occurred in a cohort of patients already treated with glucocorticoids. Our results show an agreement with those of the COV-BARRIER study, where among 370 patients with high-flow oxygen needs or on noninvasive ventilation, adding baricitinib to SOC had a significantly reduced mortality rate (17% vs 29%, HR = 0.52) [13]. In contrast with the previously published RCT of baricitinib use against SARS-CoV-2 (ACTT-2), as well as earlier observational studies, where glucocorticoid use at baseline was an exclusion criterion, our study demonstrated the adjunctive efficacy of baricitinib in patients already treated with dexamethasone [12, 18, 19]. In another study from Bangladesh where the combination was used, there was no comparison arm with patients treated only with dexamethasone [20]. Tofacitinib, another JAKi, has shown promising results in one randomized trial of 289 hospitalized patients, the majority of whom (89.3%) were receiving glucocorticoids. In a course of up to 14 days, compared with placebo, tofacitinib reduced the composite outcome of death and respiratory failure at 28 days (18% versus 29%, relative risk = 0.63). A trend towards lower mortality was also noted (2.8% versus 5.5%, HR = 0.49), albeit not statistically significant [21].

A significant body of evidence has been mounted over the years regarding the safety of chronic JAKi therapy in patients with rheumatic diseases. Janus kinase inhibitors seem to have similar risk with tumor necrosis factor-α inhibitors for serious infections, with the exception of higher risk for herpes zoster [22] and with a safety signal of higher risk for VTE with tofacitinib after weeks to months of exposure and in the presence of additional risk factors [23].

Regarding the safety of baricitinib administered for a rather short period of time (up to 14 days) and in combination with dexamethasone, we did not observe any worrisome safety signals. Infection rates had no apparent increase in the baricitinib cohort despite concomitant use of 2 immune-modifying agents. Venous thromboembolism had an incidence of 2.03/1000 patient-days in the combination versus none in SOC group. Considering the other major trials examining the use of JAK inhibitors for COVID-19, the tofacitinib and ACTT-2 studies showed no increase in secondary infections and VTE events [12, 21], whereas in the COV-BARRIER study, adding baricitinib to SOC resulted in similar rates of treatment-related infections (16%) and thromboembolic events (3%) between the baricitinib and the placebo group [13].

High-flow nasal cannula has been used as an oxygenation mode in COVID-19 respiratory failure, and in this study we show that its use was associated with a lower risk for the composite outcome. Its use is mostly guided by evidence from non-COVID-19 acute hypoxemic respiratory failure [24]. Although data from retrospective and prospective studies with this oxygenation mode showed increased ventilator-free days, in-hospital all-cause mortality remained unchanged [25, 26]. Both European Respiratory Society [27] and Surviving Sepsis Campaign [28] suggest the use of HFNC over other modes of noninvasive ventilation; however, the quality of evidence and the strength of these recommendations are low.

Our findings are strengthened by the real-life setting of consecutive patients, a recent control group, a rather consistent treatment algorithm, low proportion of missing data, and a homogenous cohort in terms of disease severity.

Limitations are its retrospective design, the absence of contemporary controls treated with SOC, and probable confounders or the presence of other confounders such as the dosing regimen of LMWH. Regarding the former, we recognize the shortcomings of observational studies, as they were recently reviewed by Tleyjeh et al [29]. However, we do believe that the serial inclusion of patients and the IPWR analysis may have reduced the risk for bias. The absence of contemporary controls could also add a bias given the changes in clinical care over time. Nevertheless, the only notable change in clinical care between the 2 periods was the more widespread availability of high-flow nasal cannula in both hospitals, and this was the reason for including mode of oxygenation before intubation in our analysis. We cannot also exclude the chance of residual confounding due to comorbidities; however, in our case, the difference in Charlson comorbidity index between the 2 outcome groups was mainly driven by their 10-year age difference. Coagulation disorders in COVID-19 are recognized as important pathways

in the pathophysiology of the disease with immunothrombosis having an integral role especially in patients with severe disease [30]. Optimal dosing is not well defined, and recent controlled trials offered discordant results with the use of therapeutic dosing in noncritically and critically ill patients [31, 32]. Given the fact that our study population included both noncritically and critically patients, we cannot conclude to what extent the different anticoagulation strategies had an impact on our results. Finally, although we did not observe any clinically significant safety signal between the 2 treatment regimens during hospitalization, we cannot rule out the possibility of a difference in adverse events occurring shortly after discharge.

CONCLUSIONS

Taken together, our real-life study shows evidence of a survival benefit in patients with sCOVID-19 treated with the combination of baricitinib and SOC regimen without any significant short-term safety issues.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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