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Predictive risk factors for hospitalization and response to colchicine in patients with COVID-19

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ABSTRACT

Objective: A predictive model for hospitalization due to COVID-19 or death was developed in the placebo group (N=2,084) from a large clinical trial of colchicine in COVID-19 patients (N = 4,159).
Results: The 7 variables retained in the predictive model were age, gender, body-mass index, history of respiratory disease, use of diabetes drugs, use of anticoagulants, and use of oral steroids at the time of randomization. An optimal threshold value identified from the predictive model was used to classify high-risk patients (those with a predicted probability above the optimal threshold) and low-risk patients (those with a predicted probability below the optimal threshold). The number needed to treat to prevent 1 hospitalization or death with colchicine treatment decreased from 71 in the whole study population (N = 4,159) to 29 in the high-risk subgroup (N=1,692).
Conclusion: This model could serve to identify high-risk subjects who will particularly benefit from early colchicine therapy.

Background

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) responsible for the COVID-19 pandemic has resulted in more than 5 million deaths since its initial identification in Wuhan, China, in December 2019. As of January 2022, there were a few antivirals approved for the treatment of this new coronavirus: 2 polymerase inhibitors (remdesivir and molnupiravir) and 1 protease inhibitor (paxlovid). The Colcorona study (ClinicalTrials.gov: NCT04322682) was a randomized, double-blind trial in which COVID-19 community-treated subjects were randomized to receive either colchicine (0.5 mg BID for 3 days and once daily thereafter) or placebo for 30 days. The primary efficacy endpoint of this study was the composite of hospitalization due to COVID-19 or death in the first 30 days after randomization. Among the 4,159 patients with RT-PCR-confirmed COVID-19 infection, the primary endpoint occurred in 4.6% and 6.0% of patients in the colchicine and placebo groups, respectively (OR = 0.75, 95% CI = 0.57-0.99, p-value = 0.04) (Tardif et al, 2021). In the whole population, the number needed to treat (NNT) to prevent 1 hospitalization due to COVID-19 or death was 71.

Objectives

The objective of the present study was to determine risk factors for hospitalization or death in ambulatory COVID-19 subjects and subsequently to identify high-risk patients who will more greatly benefit from early colchicine therapy.

Methods

A stepwise multivariable logistic regression model with potential risk factors was tested in the placebo group (N = 2,084). The criterion for a variable to enter the model was a p-value less than 0.25, and to stay in the model was a p-value less than 0.10. The resulting model was further evaluated on clinical grounds, and the C-statistic was determined for the final predictive model as well as the optimal threshold value for the predicted probability according to Youden's index. A 10-fold cross-validation to internally validate the final model was performed on the 2,084 placebo patients.

Individual risk scores and their predicted probability were calculated for the overall cohort of 4,159 subjects according to the

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Table 1
Beta coefficients for the variables retained in the final predictive model derived in the placebo group

Variables	Beta coefficients
Intercept	β_0 = -7.0403
age (x_1)	β_1 = 0.0334
sex (x_2)	β_2 = 0.8821
body mass index (x_3)	β_3 = 0.0492
history of respiratory disease (x_4)	β_4 = 0.4557
use of diabetes drugs (x_5)	β_5 = 0.5013
use of anticoagulants (x_6)	β_6 = 0.8644
use of oral steroids (x_7)	β_7 = 1.6643

beta coefficients of the final predictive model derived in the placebo group and their individual values of the retained risk factors. The optimal threshold value identified from the final predictive model in the placebo group was used to classify high-risk patients (those with a predicted probability above the optimal threshold) and low-risk patients (those with a predicted probability below the optimal threshold). Finally, a subgroup analysis using a logistic regression model including the treatment group (colchicine/placebo), the risk subgroup variable (high-risk/low-risk), and the treatment group by risk subgroup variable interaction was performed.

Results

The 7 variables retained in the predictive model for hospitalization due to COVID-19 or death in the placebo group were age, sex, body-mass index, history of respiratory disease, use of diabetes drugs, use of anticoagulants, and use of oral steroids at the time of randomization. This final predictive model had a C-statistic of 0.718 and the optimal threshold value; that is, the cut-off for the predicted probability that maximizes the sensitivity and specificity was 0.0516. The average C-statistic of the 10-fold cross-validation was 0.710, therefore showing good predictive performance.

The individual risk scores were calculated for the overall cohort of 4,159 subjects using the following equation:

$$\text{riskscore} = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \beta_4 x_4 + \beta_5 x_5 + \beta_6 x_6 + \beta_7 x_7$$

where β_i are the beta coefficients for the variables (x_i) retained in the final predictive model in the placebo group as shown in Table 1.

The individual predicted probability of hospitalization due to COVID-19 or death for the overall cohort of 4,159 subjects was then obtained based on the equation of logistic regression:

$$p = \exp(\text{riskscore})/(1 + \exp(\text{riskscore}))$$

Each of the 4,159 subjects was then classified based on their individual predicted probability of hospitalization due to COVID-19 or death "p" and using the optimal threshold value of 0.0516 as:

High-risk patient if p >= 0.0516
Low-risk patient if p < 0.0516

The composite of hospitalization due to COVID-19 or death broken down by risk subgroup (high-risk/low-risk) is shown in Table 2. In the low-risk subgroup (N = 2,455), the primary outcome occurred in 2.9% and 2.9% of patients in the colchicine and placebo groups, respectively (OR = 1.01, 95% CI = 0.63-1.63, p-value = 0.95). In the high-risk subgroup (N = 1,692), the primary outcome occurred in 7.1% of patients in the colchicine group and 10.6% of patients in the placebo group (OR = 0.64, 95% CI = 0.46-0.91, p-value = 0.01). The NNT to prevent 1 hospitalization or death with colchicine treatment decreased from 71 in the whole study population (N = 4,159) to 29 in the high-risk subgroup (N=1,692).

Men and women represented 80% and 20% of high-risk subgroup patients, respectively. Almost all high-risk women had at least 2 risk factors among the following: use of diabetes drugs, history of respiratory disease, use of oral steroids, use of anticoagulants, age ≥ 65 years, and body-mass index ≥ 30 kg/m^2. For men, only 1 risk factor among the above was necessary to be part of the high-risk subgroup.

Discussion

In the present study, we have developed a simple predictive model based on clinical data and medications that allows the identification of nonhospitalized subjects with COVID-19 who will benefit the most from early colchicine therapy. Colchicine is a potent anti-inflammatory drug currently used for the treatment of gout, pericarditis, and familial Mediterranean fever. This medication has been shown to inhibit the inflammasome pathway that is activated in COVID-19 patients, and the subsequent cytokine storm (Pope and Tschopp, 2007, Rodrigues et al, 2021). Meta-analyses based on randomized clinical trials and retrospective studies have suggested that colchicine may reduce hospitalization, length of stay, and mortality in ambulatory COVID-19 subjects (Deftereos et al, 2020, Elshafei et al, 2021, Lopes et al, 2021, Nawangsih et al, 2021, Tardif et al, 2021). The risk factors for severe disease or death reported in our study are in line with several other studies performed in France (Bonnet et al, 2021), the United States (Suleyman et al, 2020), and in the province of Ontario, Canada (Snider et al, 2021). In particular, risk factors such as male gender, advanced age, diabetes, and severe obesity have been reported in those studies.

Our study has some limitations. First, the study participants were enrolled before the emergence and dissemination of SARS-CoV-2 variants of concern and widespread vaccination. It is possible that risk factors may vary according to specific variants and vaccination status. Also, our model is mainly predictive of hospitalization because there were few deaths (N = 14) in the Colcorona trial. Finally, some risk factors (e.g., minority groups <7%) may not have been identified because of their low occurrence in this trial.

In conclusion, a simple clinical model (which includes age, sex, body-mass index, history of respiratory disease, and use of diabetes drugs, anticoagulants, and oral steroids at the time of disease onset) predicts the risk of hospitalization or death in nonhospitalized patients with early COVID-19. Men with 1 other risk factor and women with at least 2 risk factors should be considered for

Table 2
Primary outcome (hospitalization due to COVID-19 or death) broken down by risk subgroups

Subgroup basedon risk score[1]	Primaryendpoint	Placebo(N=2084)	Colchicine(N=2075)	Odds ratio (95% CI); p-value
Low-risk ($p^1 < 0.0516$)	N	1219	1236	2455
	No	1184 (97.1%)	1200 (97.1%)	1.01 (0.63; 1.63); 0.9512
	Yes	35 (2.9%)	36 (2.9%)	
High-risk ($p^1 >= 0.0516$)	N	859	833	1692
	No	768 (89.4%)	774 (92.9%)	0.64 (0.46; 0.91); 0.0116
	Yes	91 (10.6%)	59 (7.1%)	

[1] Individual risk score and their predicted probability of hospitalization due to COVID-19 or death "p" were calculated for the overall cohort of 4,159 subjects according to the beta coefficients of the final predictive model derived in the placebo group and their individual values of the retained risk factors.

early colchicine therapy or other type of treatment, given the large benefit in these subgroups.

DISCLOSURES

Jean-Claude Tardif reports grants from the Government of Quebec, the National Heart, Lung, and Blood Institute of the United States National Institutes of Health (NIH), the Montreal Heart Institute Foundation, the Bill & Melinda Gates Foundation, Amarin, Esperion, Ionis, Servier, and RegenXBio, along with grants and personal fees from AstraZeneca, Sanofi, and Servier, and grants, personal fees, and minor equity interests from Dalcor. In addition, Jean-Claude Tardif's institution has submitted a pending patent for a method of treating a coronavirus infection using colchicine, and a pending patent on early administration of low-dose colchicine after myocardial infarction. Jean-Claude Tardif has waived his rights in all patents related to colchicine and does not stand to benefit financially if colchicine becomes used as a treatment for COVID-19. Marie-Claude Guertin and Jean-Claude Tardif have a patent method for treating or preventing cardiovascular disorders and lowering risk of cardiovascular events issued to Dalcor, no royalties received, a patent genetic marker for predicting responsiveness to therapy with HDL-raising or HDL mimicking agent issued to Dalcor, no royalties received, and a patent method for using low-dose colchicine after myocardial infarction with royalties paid to invention assigned to the Montreal Heart Institute. The other authors have no conflicts of interest to declare.

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Ethical approval

The protocol was approved by the institutional review board at all centers involved in the 6 countries that participated in the trial. COLCORONA - Full list of trial investigators with their institutional affiliations:

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