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

Running title: Risk factors for COVID-19 hospitalization

Jean-Claude Tardif¹, Mariève Cossette², Marie-Claude Guertin², Nadia Bouabdallaoui¹, Marie-Pierre Dubé¹, Guy Boivin³ on behalf of the Colcorona study group.

¹Montreal Heart Institute and Université de Montréal, Montreal, QC, Canada; ²Montreal Health Innovations Coordinating Center (MHICC), Montreal, QC, Canada; ³Research Center in Infectious Diseases, CHU de Québec and Université Laval, Quebec City, QC, Canada.

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Dr Guy Boivin, corresponding author
E-mail: Guy.Boivin@crchudequebec.ulaval.ca

Highlights:

- A predictive model for COVID-19 hospitalization or death was developed.
- This model was based on seven risk factors for COVID-19.
- This model identified high risk subjects who could benefit from colchicine therapy.
Abstract

**Objective:** A predictive model for hospitalization due to COVID-19 or death was developed in the placebo group (N=2084) from a large clinical trial of colchicine in COVID-19 patients (N = 4159). **Results:** The seven variables retained in the predictive model 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. 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 one hospitalization or death with colchicine treatment decreased from 71 in the whole study population (N = 4159) to 29 in the high-risk subgroup (N=1692). **Conclusion:** This model could serve to identify high-risk subjects who will particularly benefit from early colchicine therapy.

**Keywords:** COVID-19; colchicine; hospitalization; risk factors; sex.

Background

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) responsible for 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: two polymerase inhibitors (remdesivir and molnupiravir) and one 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 4159 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 one 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 = 2084). 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 2084 placebo patients.

Individuals risk scores and their predicted probability were calculated for the overall cohort of 4159 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. 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 seven 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, i.e. the cut-off for the predicted probability that maximises 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 individuals risk scores were calculated for the overall cohort of 4159 subjects using the following equation:

\[
\text{risk score} = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \beta_4 x_4 + \beta_5 x_5 + \beta_6 x_6 + \beta_7 x_7
\]

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

The individual predicted probability of hospitalization due to COVID-19 or death for the overall cohort of 4159 subjects where then obtained based on the equation of logistic regression:

\[
p = \frac{\exp(\text{risk score})}{1 + \exp(\text{risk score})}
\]
Each of the 4159 subjects was then classified based on its 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 \( p \geq 0.0516 \)

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 the Table 2. In the low-risk subgroup (\( N = 2455 \)), the primary outcome occurred in 2.9% and 2.9% of patients in the colchicine and placebo groups, respectively (\( OR = 1.01, 95\% CI = 0.63-1.63, p\text{-value} = 0.95 \)). In the high-risk subgroup (\( N = 1692 \)), the primary outcome occurred in 7.1% of patients in the colchicine group and 10.6% of patients in the placebo group (\( OR = 0.64, 95\% CI = 0.46-0.91, p\text{-value} = 0.01 \)). The NNT to prevent one hospitalization or death with colchicine treatment decreased from 71 in the whole study population (\( N = 4159 \)) to 29 in the high-risk subgroup (\( N=1692 \)).

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

**Discussion**

In this study, we have developed a simple predictive model based on clinical data and medications that allows the identification of non-hospitalized 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, which 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), USA (Suleyman et al., 2020) and in the province of Ontario, Canada (Snider et al., 2021). In particular, risk factors such as male sex, advanced age, diabetes and severe obesity have been reported in those studies.

Our study has some limitations. First, the study participants were enrolled prior to 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 as there were few deaths (N = 14) in the Colcorona trial. Finally, some risk factors (e.g., minority groups <7%) may not have been identified due to their low occurrence in this trial.

In conclusion, a simple clinical model (which includes age, sex, body-mass index, history of respiratory disease, use of diabetes drugs, anticoagulants and oral steroids at the time of disease onset) predicts the risk of hospitalization or death in non-hospitalized patients with early COVID-19. Men with one other risk factor and women with at least two risk factors should be considered for early colchicine therapy or other type of treatment given the large benefit in these subgroups.
Conflict of interest statement

J-CT reports grants from Government of Quebec, the National Heart, Lung, and Blood Institute of the US 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, J-CT’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. J-CT 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. M-PD and J-CT 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 markers 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 competing interests to declare.

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Ethical approval

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

Brazil: Antunes, M. Hospital Universitário Bragança Paulista, Sao Paulo; Chaves E.B.M. Hospital de Clinicas de Porto Alegre, Porto Alegre; da Luz, P.L. Instituto do Coração HCFMUSP, Sao Paulo; Mattos C. Hospital de Clínicas de Passo Fundo, Passo Fundo; Viecili, P.R.N. Instituto Cruzaltense de Cardiologia - Health Interdisciplinary Research Laboratory Group Centro, Cruz Alta; Ripardo, J.P. Hospital Samaritano Higienópolis, Sao Paulo.

Canada: Azzari, F. A. CISSS Bas Saint-Laurent – Hôpital Régional de Rimouski, Rimouski; Bérubé, S. CIUSSS de l’Estrie – Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke; Bouabdallaoui, N. Montreal Heart Institute, Montreal; Conway, B. Vancouver Infectious Diseases Research and Care Centre Society, Vancouver; Deb, S. Sunnybrook Health Sciences Center (on Ontario ICF), Toronto; Francoeur, B. CIC Mauricie, Trois-Rivières; Frenes, SE. Sunnybrook Health Sciences Center (on Ontario ICF), Toronto; Gaudet, D. Ecogene-21, Chicoutimi; Khourey, E. Ecogene-21, Chicoutimi; Lavoie-L’Allier, P. Montreal Heart Institute, Montreal; Tardif, JC Montreal Heart Institute, Montreal.

Greece: Deftereos, S. University General Hospital of Athens "Attikon", Athens; Randou, E. General Hospital of Kozani "Mamatsio", Kozani.

South Africa: Prozesky, H. Tread Research, Tygerberg Hospital, Cape Town.

Spain: Alfonso, F. Hospital Universitario de La Princesa, Madrid; Arribas, F. Hospital Universitario 12 de Octubre, Madrid; Calvin, M.E. Hospital Universitario La Paz, Madrid; Del
Val, D. Hospital Universitario de La Princesa, Madrid; Garcia Villa, A. Fundación Jiménez Díaz, Madrid; Lopez-Sendon, J. Hospital Universitario La Paz, Madrid; Lopez-Sendon Moreno, J. Hospital Universitario Ramón y Cajal, Madrid; Martin-Jimínez, ML. Hospital Universitario Puerta de Hierro, Madrid; Munoz, P. Hospital General Universitario Gregorio Marañón, Madrid; Perez Torre, P. Hospital Universitario Ramón y Cajal, Madrid; Segovia, J. Hospital Universitario Puerta de Hierro Madrid Tunon, J. Fundación Jiménez Díaz, Madrid.

United States: Al Rabadi, O. Yuma Regional Medical Center, Yuma; Baker, WF. Central Cardiology Medical Center, Bakersfield; Berney, S. University of Arkansas for Medical Sciences, Institute on Aging, Little Rock; Brodetskiy, K. Woodhull Hospital, Brooklyn; Costanzo, J. Stamford Health Stamford Hospital, CT. Spring Clinical Research, Spring, TX; Hsue, P. Zuckerberg San Francisco General Hospital, San Francisco; Joshi, A. Mayo Clinic – Rochester, Rochester; Kennish, L. Summit Medical Group, New Jersey; King, C.M. North Mississipi Medical Clinic, Tupelo; Kole A. Mayo Clinic – Phoenix, Phoenix; Leibowitz, E. Valley Health, Ridgewood; Lepor, N. Westside Medical Associates of Los Angeles, Beverly Hills; Makam, S. Newburgh Horizon/Mid Hudson Medical, New York; Matejicka, A. Montefiore Nyack Hospital, New York; Meisner, J. University of Texas Southwestern Medical Center, Dallas; Nader, R. Miami Center for Advanced Cardiology, Miami Beach; Orenstein, R. Mayo Clinic – Phoenix, Phoenix; Pillinger, M.H. NYU Grossman School of Medicine, New York; Radford, M. NYC Health and Hospitals, Hackensack Meridian Health, New York; Raiszadeh, F. Harlem Hospital, New York; Rank, M. Mayo Clinic – Phoenix, Phoenix; Rollins, N. University of Texas Southwestern Medical Center, Dallas; Schnee, A. Prisma Health – Upstate, Greenville; Shah, B. NYU Grossman School of Medicine, New York; Shaw, S. Rancho Research Institute at Rancho Los Amigos National Rehabilitation Center, Downey; Sheikh, SZ.
University of North Carolina at Chapel Hill, Chapel Hill; Shue, P. University of California San Francisco, San Francisco; Speicher, L. Mayo Clinic – Jacksonville, Jacksonville; Szerlip, HM. Baylor Scott & White Research Institute, Dallas; Yang, F. Maimonides Hospital, New York; Yanez, G. South Florida Research Organization, Miami.

References


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

<table>
<thead>
<tr>
<th>Variables</th>
<th>Beta coefficients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>$\beta_0 = -7.0403$</td>
</tr>
<tr>
<td>age ($x_1$)</td>
<td>$\beta_1 = 0.0334$</td>
</tr>
<tr>
<td>sex ($x_2$)</td>
<td>$\beta_2 = 0.8821$</td>
</tr>
<tr>
<td>body mass index ($x_3$)</td>
<td>$\beta_3 = 0.0492$</td>
</tr>
<tr>
<td>history of respiratory disease ($x_4$)</td>
<td>$\beta_4 = 0.4557$</td>
</tr>
<tr>
<td>use of diabetes drugs ($x_5$)</td>
<td>$\beta_5 = 0.5013$</td>
</tr>
<tr>
<td>use of anticoagulants ($x_6$)</td>
<td>$\beta_6 = 0.8644$</td>
</tr>
<tr>
<td>use of oral steroids ($x_7$)</td>
<td>$\beta_7 = 1.6643$</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Subgroup based on risk score $^1$</th>
<th>Primary endpoint</th>
<th>Placebo (N=2084)</th>
<th>Colchicine (N=2075)</th>
<th>Odds ratio (95% CI); p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-risk ($p^1 &lt; 0.0516$)</td>
<td>N</td>
<td>1219</td>
<td>1236</td>
<td>2455</td>
</tr>
<tr>
<td>No</td>
<td>1184 (97.1%)</td>
<td>1200 (97.1%)</td>
<td>1.01 (0.63; 1.63); 0.0116</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>35 (2.9%)</td>
<td>36 (2.9%)</td>
<td>0.9512</td>
<td></td>
</tr>
<tr>
<td>High-risk ($p^1 \geq 0.0516$)</td>
<td>N</td>
<td>859</td>
<td>833</td>
<td>1692</td>
</tr>
<tr>
<td>No</td>
<td>768 (89.4%)</td>
<td>774 (92.9%)</td>
<td>0.64 (0.46; 0.91); 0.0116</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>91 (10.6%)</td>
<td>59 (7.1%)</td>
<td>0.0116</td>
<td></td>
</tr>
</tbody>
</table>

$^1$ Individual risk score and their predicted probability of hospitalization due to COVID-19 or death “p” were calculated for the overall cohort of 4159 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.