Predictors of Long COVID-19 in Patients with Severe Disease – A US Healthcare Database Analysis

Chantal Holy[1], Brandon Patterson[2], Jill Ruppenkamp[1], Fayolah Richards[2], Ronita Debnath[3], Jessica K. DeMartino[4], Brahim Bookhart[4], Antoine C. El Khoury[2], Paul M. Coplan[1]

1: Epidemiology & Real-World Data Sciences, Johnson & Johnson MEDTECH, New Brunswick, NJ - USA
2: Janssen Global Services, Raritan, NJ - USA
3: Mu Sigma, Bangalore – India
4: Janssen Scientific Affairs, Titusville, NJ - USA

Introduction

- Continued morbidity following COVID-19 (long COVID (LC)) is defined by the World Health Organization (WHO) as conditions lasting > 2 months and identified approximately 3 months after COVID-19 onset.[1]
- Similarly, the United Kingdom National Health Services describes Post-COVID-19 syndrome (PCS), as the persistence of COVID-19 symptoms beyond 12 weeks.[2]
- Predictors for PCS following COVID-19 infection are not known.

Objective

- Develop a machine learning method to predict patients at risk for PCS following severe COVID-19.

Methods

- **Database:** IBM® MarketScan® Commercial and Medicare Supplemental databases
- **Population:** Patients with COVID-19 (first date = index) from April 1, 2020 to June 30, 2021 were stratified by severity (mild, moderate and severe/critical (SC)), based on the Janssen Phase 3 ENSEMBLE Clinical Trial definition of severity.[3] Only SC patients were included in this analysis.
- **Outcome:** Duration of disease was defined as follows: from 5 days before positive test to last related visit/prescription, with a maximum gap of 35 days between visits/prescriptions. The study outcome was PCS (duration > 84 days) vs no PCS.
- **Variables** included demographics, comorbidities (Elixhauser index (EI) and all 31 Elixhauser disease domains), and all CSS during index disease, as well as treatments received during the inpatient care.
- **Modeling:** 64 machine learning algorithms were evaluated to develop prediction models using the DataRobot platform. Specifically:
  - Data was subdivided as follows: 20% of the data was set aside as a holdout dataset, the remaining 80% was subdivided in 5 cross-validation partitions.
  - All models were trained on one cross-validation fold. For the highest performing models, the subset sizes were increased. The best models completed 5-fold cross-validation training and scoring. Scoring was done using LogLoss. The holdout data was then used to validate model performance.
- **An Ensemble model** (Blender) was generated, using the best available algorithms. The purpose of the Ensemble model was to maximize model accuracy (vs speed).

Results

- A total of 34,317 patients were analyzed, as shown in Table 1.
- Features included: Demographic variables (age, gender, region of the US), comorbidities (31 Elixhauser chronic diseases and additional chronic conditions), CSSs and COVID-19 treatments.
- The highest accuracy was obtained from an Average Blender (AVG BLENDER) model. This model took predictions from 8 individual algorithms as shown in Figure 1. The LogLoss scores for the AVG Blender were as follows: cross-validation: 0.4279; holdout: 0.4187; validation: 0.4252.
  - Key features affecting AVG Blender are shown, in order of importance, in Figure 2.
  - The AVG Blender model performance is shown in Figure 3.

Table 1 : Key demographics of population used for modeling

	Severe - No PCS	Severe - with PCS
N	27,628	6,689
Age (mean (SD))	54.73 (14.63)	59.09 (15.35)
Female (vs Male)	12,099 (43.8%)	3,135 (46.9%)
payer = Medicare (%)	4,899 (17.7%)	1,913 (28.6%)
Elixhauser Index (mean (SD))	1.96 (2.17)	2.98 (2.84)

Figure 1 : Blueprint of Average Blender model for predicting PCS in Patients with SC COVID-19. Eight distinct algorithms were selected from 64 algorithms, based on lowest LogLoss. The predictions from these models were averaged together in the Average Blender.

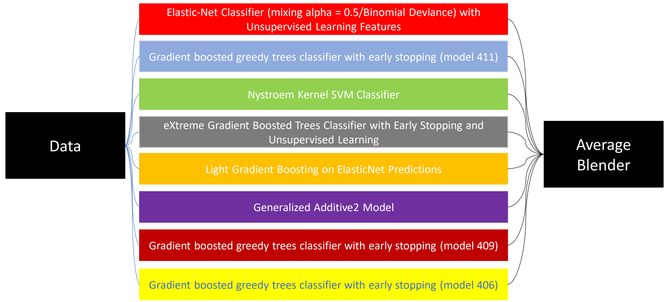

Figure 2: Top 12 Feature impact on Average Blender model. From a CSS standpoint, malaise, hypoxemia, and thrombosis were key features. As expected, variables often associated with SC disease, such as ICU admission and ventilator use, were also among the top 12 features identified.

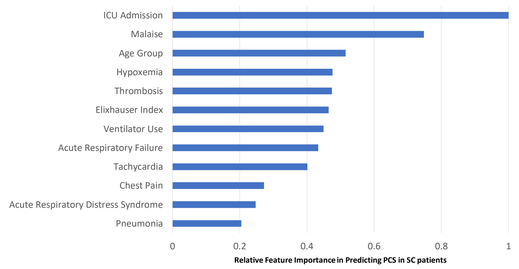

Figure 3: Average Blender Model Performance. The model achieved high negative predictive value (0.8907), but low positive predictive value (0.3713).

Key Findings

- **Predictive models to evaluate risk for Post-COVID-19 Syndrome were developed, in a population with severe COVID-19.**
- **Approximately 20% of the severe population developed Post-COVID-19 Syndrome.**
- **Key predictors included malaise, hypoxemia and thrombosis at time of acute disease.**

Conclusions

- **The Ensemble model achieved high negative predictive value (0.8907), but low positive predictive value (0.3713), highlighting the difficulty in predicting who will suffer from Post-COVID-19 Syndrome in the severe COVID-19 patient population.**

References:

1. https://www.who.int/publications/i/item/WHO-2019-nCoV-Post_COVID-19_condition-Clinical_case_definition-2021.1 - Last accessed 04/04/2022
2. https://www.nhs.uk/conditions/coronavirus-covid-19/long-term-effects-of-coronavirus-long-covid/ - Last accessed 04/04/2022
3. https://www.jnj.com/coronavirus/ensemble-1-study-protocol – Last accessed 04/04/2022

Abbreviations:

COVID-19: Coronavirus disease 2019
CSS: COVID-19 signs and symptoms
LC: Long COVID
PCS: Post-COVID-19 Syndrome
ICU: Intensive Care Unit
EI: Elixhauser index
SC: Severe/Critical
SD: Standard deviation

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