Development and validation of multivariable prediction models for adverse COVID-19 outcomes in IBD patients

John Sperger, BS[1], Kushal S. Shah, BS[1], Minxin Lu, BS[1], Xian Zhang, PhD[2], Ryan C. Ungaro, MD, MS[3], Erica J. Brenner, MD[2], Manasi Agrawal, MD[3], Jean-Frederic Colombel, MD[3], Michael D. Kappelman, MD, MPH[2], Michael R. Kosorok, PhD[1]

[1]Department of Biostatistics, University of North Carolina, Chapel Hill, NC

[2] Division of Pediatric Gastroenterology, Department of Pediatrics, University of North Carolina, Chapel Hill, NC

[3] The Henry D. Janowitz Division of Gastroenterology, Icahn School of Medicine at Mount Sinai, NY

Corresponding author: John Sperger. jsperger@live.unc.edu

Attn: John Sperger
Biostatistics, McGavran-Greenberg Hall, CB#7420
Chapel Hill, NC 27599

Word count: 2874

Key Points

Question How well can a multivariable risk model predict the risk of hospitalization, intensive care unit (ICU) stay, or death due to COVID-19 in patients with inflammatory bowel disease (IBD)?

Findings Multivariable prediction models developed using data from an international voluntary registry of IBD patients and available for use online (https://covidibd.org/) have very good discrimination for predicting hospitalization (Test set AUC 0.79) and excellent discrimination for ICU admission (Test set AUC 0.88) and death (Test set AUC 0.94). The models were developed with a training sample of 2009 cases and validated in an independent test sample of 700 cases comprised of a random sub-sample of cases and all cases-entered in the registry during a one-month period after model development.

Meaning This risk prediction model may serve as an effective tool for healthcare providers to facilitate conversations about COVID-19-related risks with IBD patients.

Structured Abstract

Importance

Risk calculators can facilitate shared medical decision-making[1]. Demographics, comorbidities, medication use, geographic region, and other factors may increase the risk for COVID-19-related complications among patients with IBD[2,3].

Objectives

Develop an individualized prognostic risk prediction tool for predicting the probability of adverse COVID-19 outcomes in patients with IBD.

Design, Setting, and Participants

This study developed and validated prognostic penalized logistic regression models[4] using reports to Surveillance Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease (SECURE-IBD) from March–October 2020. Model development was done using a training data set (85% of cases reported March 13 – September 15, 2020), and model validation was conducted using a test data set (the remaining 15% of cases plus all cases reported September 16–October 20, 2020).

Main Outcomes and Measures

COVID-19 related:

1. Hospitalization+: composite outcome of hospitalization, ICU admission, mechanical ventilation, or death

2. ICU+: composite outcome of ICU admission, mechanical ventilation, or death

3. Death

We assessed the resulting models' discrimination using the area under the curve (AUC) of the receiver-operator characteristic (ROC) curves and reported the corresponding 95% confidence intervals (CIs).

Results

We included 2709 cases from 59 countries (mean age 41.2 years [s.d. 18], 50.2% male). A total of 633 (24%) were hospitalized, 137 (5%) were admitted to the ICU or intubated, and 69 (3%) died. 2009 patients comprised the training set and 700 the test set.

The models demonstrated excellent discrimination, with a test set AUC (95% CI) of 0.79 (0.75, 0.83) for Hospitalization+, 0.88 (0.82, 0.95) for ICU+, and 0.94 (0.89, 0.99) for Death. Age, comorbidities, corticosteroid use, and male gender were associated with higher risk of death, while use of biologic therapies was associated with a lower risk.

Conclusions and Relevance

Prognostic models can effectively predict who is at higher risk for COVID-19-related adverse outcomes in a population of IBD patients. A free online risk calculator (https://covidibd.org/covid-19-risk-calculator/) is available for healthcare providers to facilitate discussion of risks due to COVID-19 with IBD patients. The tool numerically and visually summarizes the patient's probabilities of adverse outcomes and associated CIs. Helping physicians identify their highest-risk patients will be important in the coming months as cases rise in the US and worldwide. This tool can also serve as a model for risk stratification in other chronic diseases.

Introduction

Since the onset of the novel coronavirus disease 2019 (COVID-19) pandemic, almost 50
million cases have been reported globally. Many countries, including the United States
(US), are reporting record numbers of new cases as of November 2020[5]. While the majority
of cases are mild, patients with at least one comorbidity are at higher risk of adverse
outcomes, including hospitalization, respiratory failure, or death[6,7]. Risk calculators can
facilitate shared decision making between patients and healthcare providers[1], and such
tools have been created to predict death due to COVID-19 in US patients 65 years and
older[8], to determine hospitalization risk[9], and to guide early vaccine allocation.

Patients with inflammatory bowel disease (IBD) are prescribed immunosuppressive
medications such as corticosteroids, immunomodulators, biologic therapies, and Janus-
kinase inhibitors, which are linked with a higher risk of viral infection[10,11]. To help
healthcare providers and patients navigate these myriad potential risk factors, we
developed and validated penalized multivariable logistic regression models for predicting
the probability of hospitalization, intensive care unit (ICU) admission, and death due to
COVID-19 in patients with IBD. We utilized an international registry of 2,709 IBD patients
with COVID-19 from 59 countries. We also developed a free, publicly available
personalized risk calculator utilizing the final models that is available online
(https://covidibd.org/covid-19-risk-calculator/). Reporting follows Transparent reporting of a
multivariable prediction model for individual prognosis or diagnosis (TRIPOD)[12]
guidelines.

Methods

Source of Data

The Surveillance Epidemiology of Coronavirus Under Research Exclusion for Inflammatory
Bowel Disease (SECURE-IBD) database (www.covidibd.org) is an international registry to
study outcomes of COVID-19 in pediatric and adult IBD patients[13]. SECURE-IBD is a
voluntary registry with ongoing data collection where healthcare providers can report
cases of COVID-19 in IBD patients, confirmed by polymerase chain reaction (PCR) or
antibody testing. Healthcare providers are instructed to report cases of severe outcomes
after a minimum of seven days from the onset of symptoms and after a sufficient time has
passed to observe the disease course through the resolution of acute illness or death. In the
event that a patient's status changed after submission, reporters are instructed to re-report
and contact the research team. Reporters were not explicitly informed of what data could
be used as predictors or outcomes, but being a voluntary registry, reporters were not
blinded. A fuller account of the data collection is given in Brenner et al. (2020)[14].

Participants

We included all patients reported to the registry from March 13, 2020, the data collection
start date, through October 20, 2020. For model development, a training sample consisting
of 85% of the entire surveillance data set available as of September 15, 2020 was used. The
random split was done using stratified random sampling based on an ordinal version of the
outcome. The test data set consisted of the remaining 15% of the data available on
September 15, plus all of the additional cases reported to the registry between September
16, 2020 and October 20, 2020.

We reported means and standard deviations for continuous variables, counts for

categorical variables, and proportions for binary variables. We reported the missing data

for all variables. We did not include *P* values in our descriptive tables following the

Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)

guidelines[15].

Outcomes

We examined three primary outcomes: 1) hospitalization or death (Hospitalization+), 2)

ICU admission, mechanical ventilation or death (ICU+), and 3) death due to COVID-19

related causes (Death). Patients may experience multiple outcomes. All outcomes were

reported by the patient's healthcare provider at the time of the case report.

Predictors

As our aim was to create models and a risk stratification tool intended to allow physicians

to inform patients of their risk before presenting with COVID-19, we restricted our

attention to predictors that would be available during a routine consultation. COVID-19

presenting symptoms and information about the COVID-19 treatment received were

therefore not included in this analysis. All predictors were reported by the patients'

healthcare provider.

A full description of the predictors is available in **Supplement document eTable 1.**

Demographic predictors included age, country of residence, state of residence (for US

cases), gender, race, and ethnicity. Racial indicators included White, Black, and Asian.

American Indian and Pacific Islander indicators were excluded due to low prevalence.

Multi-racial patients belong to multiple categories. As only one patient had reported a

7

gender other than male or female, only two genders were considered in the analysis. Due to the nature of reporting, ethnicity, gender, and race should be interpreted as provider-perceived race and gender. Assessing race and ethnicity is important for identifying potential health inequities in COVID-19 related outcomes. For cases from US states with very low prevalence in the registry, a more general geographic predictor (census region or census division) was used in place of the state itself. Clinical predictors included height, weight, body mass index (BMI, study derived), IBD diagnosis [Crohn's disease (CD), ulcerative colitis (UC), or IBD unspecified (IBDU)], and IBD disease activity as defined by physician global assessment. We also included IBD medication indicators for overall drug category (e.g., biologic therapy) and subcategory [e.g., anti-tumor necrosis factor (TNF)] at the time of COVID-19 diagnosis. Additionally, dosage information was included for prednisone, 6-mercaptopurine, and azathioprine.

For categorical (including binary) predictors without a meaningful reference level, all levels were included in the model. Quadratic terms were considered for all continuous covariates. Interactions were considered based on a combination of subject matter expert advice and a minimum threshold of thirty observations for every cell for interactions involving two binary predictors.

Missing Data

Multiple imputation[16] of the covariates and outcomes was performed using multivariate imputation by chained equations (MICE)[17] to address missing data. A total of thirty imputed data sets were created. Imputation was performed separately on the training and test data to prevent inducing dependence between the training and the test data through the imputation models. For transformed variables that are derived from other covariates

(e.g., BMI from height and weight), we imputed the missing root variables and then created
the transformed variable to ensure that the relationship between the transformed variable
and its inputs was preserved.

Table 1 includes the level of missing data in each of the covariates included in the analysis.
Medication variables, clinical descriptions of disease and severity, location, age, and gender
all had very low levels of missingness, ranging from zero to under five percent. There were
three covariates with a moderate amount of missing data — height, weight, and ethnicity
were missing in approximately 20% of patients.

Statistical Analysis

The 10-fold cross-validation deviance averaged across each of the imputed data sets was
used to decide between LASSO, Ridge, or Elastic net penalties and to choose the value of the
regularization parameter[4,18]. Separate logistic regression models were fit for each of the
outcomes. Smoothing splines for continuous covariates[19], a multinomial model, Group
LASSO[20], and Sparse Group LASSO[21] were all investigated as potential methods, but the
performance improvement in terms of the cross-validation deviance was not sufficient to
justify the additional complexity and computational time. The nonparametric resampling
bootstrap was used to generate 1,000 samples, and for each bootstrap sample, the same
sampled participants were used across the 30 imputed data sets[22]. A total of 30,000
(30 × 1000) fitted models were created. Predicted probabilities were created by averaging
the predictions from all models. We used the sample mean of the bootstrap distribution of
the predicted probabilities for the final predicted probability and the percentiles of the
bootstrap distribution to find the 90% confidence interval for the risk estimate. Risk
groups were not created.

To assess the performance of the resulting predictions, we created Receiver Operator

Characteristic (ROC) curves and calculated the corresponding area under the curve (AUC)

using the held-out test data set for the imputed data sets[22]. We provide two graphical

summaries of the resulting models: 1) a summary of the sign distribution showing, across

bootstrap replications and imputed data sets, the proportion of estimated associations

which were negative (better outcomes), zero, or positive, and 2) box plots of the estimated

effect on the log-odds scale. We opted to show box plots instead of confidence intervals to

highlight the exploratory nature of the results for individual predictors. Lasso estimates are

biased, and the lack of a priori hypotheses makes statistical significance testing

inappropriate. We first defined a set of contrasts in order to make meaningful comparisons

while accounting for the second-order terms in the model rather than report results for

every parameter. The contrast matrices are available on a public repository

https://github.com/KosorokLab/CovidIBDRiskCalc in a CSV format.

Predictions are averaged over bootstrap replications and imputed data sets, and so there is

no single set of model coefficients to report. Because the logistic link function is non-linear,

the predicted probability from averaging over predictions from each fitted model does not

equal the predicted probability from averaging over coefficients across the models.

Additionally, averaging the model coefficients would result in none of the coefficients being

equal to zero unless that coefficient is equal to zero in *every* fitted model. Instead of

reporting a misleading model summary, we opted to make all the model coefficients

available online (https://github.com/KosorokLab/CovidIBDRiskCalc).

Software

The analysis was conducted using R[23] version 4.0.2 and the tidyverse[24], glmnet[25],

glmnetUtils[26], mice[17], magrittr[27], future[28], and pROC[29] packages. The online calculator was

created using shiny[30]. The most recent draw for the Carolina Pick 4 lottery

(https://nclottery.com/Pick4) at the time of analysis was used for the random number

generation seed. The code used to conduct the analysis is available on GitHub

(https://github.com/KosorokLab/CovidIBDRiskCalc). This does not include the study data,

but the estimated model coefficients are available.

Results

Participants

A total of 2,709 patients were reported to the registry, split into a training set of 2009

patients and a test data set of 700 patients. The test data set was comprised of 366 from the

15% split and 334 patients added to the registry after model fitting and before manuscript

submission. Table 1 provides demographic, clinical, medication, and outcome descriptive

summaries for the training set, test set, and the whole sample. A total of 633 (24%) patients

were hospitalized, 137 (5%) were admitted to the ICU or intubated, and 69 (3%) patients

died. The cohort has 1076 (40%) patients from the United States, with the rest coming

from a variety of other countries summarized in Table 1.

Model Performance

The models have excellent discrimination, with an AUC and associated 95% confidence

interval estimated on the test data set averaged over the imputations of 0.79 (0.75, 0.83)

for Hospitalization+, 0.88 (0.82, 0.95) for ICU+, and 0.94 (0.89, 0.99) for death.

Predictors of hospitalization, intensive care, and death

11

Figures 1 & 2 show the estimated coefficient sign distribution and the effect on the log-odds scale for the ten contrasts most strongly associated with each outcome respectively. Consistent with other studies[7,31] on risk factors for hospitalization and death, we find older age, male gender, and comorbidities to be associated with worse outcomes due to COVID-19. White race is associated with a lower risk of Hospitalization+ in 89.2% of our replications but is not consistently selected in the models for ICU+ (30%) or death (10%). These plots, not restricted to the top ten effects, are available in the supplement for all demographic, clinical, and medication predictors (eFigures 1 & 2), for countries (eFigures 3 & 4), and for US regions (eFigures 5 & 6).

Corticosteroids are associated with a higher risk of Hospitalization+, ICU+, and death. Oral corticosteroid use is the most important predictor, in terms of the magnitude of the absolute value of the coefficient, for Hospitalization+, ICU+, and death (Figure 2). Biologic medicines are associated with a lower risk of Hospitalization+, ICU+, and death, with integrin antagonists having directionally smaller effects than tumor necrosis factor (TNF) antagonists or interleukin (IL) 12/23 inhibitors.

Online Risk Tool

The online risk calculator where physicians can enter their patient's information and receive predictions from our models is freely available at (http://shiny.bios.unc.edu/secure-ibd-risk-calc/). The *SECURE-IBD COVID-19 Risk Calculator* was designed for physicians to use during consultations with their patients and includes detailed clinical characteristics, including demographics, disease diagnosis information, comorbidities, and current medications. Daily dosage may optionally be entered for certain medications. The output of the risk calculator numerically and visually

summarizes the patient's probabilities of adverse outcomes and associated prediction

intervals among the three nested outcomes discussed earlier. Figure 3 displays the results

for two example patients and their associated probabilities (and 90% confidence intervals)

of adverse outcomes if they were to contract COVID-19. The interactive application could

provide a reliable basis for distinguishing between high- and low-risk patients to aid in

personalizing clinical guidance on decisions about precautions, returning to normal

activities, and vaccination.

Discussion

We developed and validated risk prediction models for hospitalization, intensive care stay,

and death resulting from COVID-19 in patients with IBD using data from 2,709 cases from

59 countries reported through an international voluntary registry. [13]. The models

demonstrated excellent discrimination, with a test set AUC (95% CI) of 0.79 (0.75, 0.83) for

Hospitalization+, 0.88 (0.82, 0.95) for ICU+, and 0.94 (0.89, 0.99) for Death. We made a free

online risk calculator utilizing these models (https://covidibd.org/covid-19-risk-

calculator/) for healthcare providers to facilitate discussion of risks due to COVID-19 with

their IBD patients[1]. The interactive application could provide a reliable basis for

distinguishing between high- and low-risk patients to aid in personalizing clinical guidance

on decisions about precautions, returning to normal activities, and vaccination.

Other COVID-19-related risk prediction tools have focused on predicting hospital course

based on clinical data captured at the time of admission[9] and predicting mortality among

US patients aged 65 years and older[8]. Our risk tool is unique in at least three ways. First,

we focus on a specialized population of patients with IBD, a chronic, immune-mediated

condition frequently treated with immune suppressive medications and often affected by

13

other comorbidities. Second, our model focuses on predictors that are known before a

patient were to contract COVID-19 and thus can be used to inform lifestyle or treatment

decisions to prevent infection or downstream complications. Finally, we examine a

broader range of outcomes than tools focused solely on mortality. Our work can serve as a

model for other disease areas, and our code is publicly available and could be adapted for

similar online risk tools in other settings or populations.

Strong associations with worse adverse COVID-19 outcomes were oral corticosteroids,

older age, comorbidities, gender, and white physician-reported race (for Hospitalization+).

Caution must be used when interpreting penalized regression results because the

coefficients are biased, but the results for oral corticosteroids were particularly dramatic.

Compared to not taking an oral corticosteroid, taking a daily dose equivalent of 40mg of

prednisone was associated with a ten times greater adjusted odds of death. Biologic

therapies were associated with a lower risk of adverse COVID-19 outcomes, with small

differences between the subcategories of biologic therapies. Compared to not taking a

biologic therapy, TNF inhibitors were associated with an adjusted odds ratio of 0.62 for

death. In contrast to earlier studies using this database[14,32], we did not find a consistent

association between 5-aminosalicylates and a higher risk of adverse outcomes; depending

on the imputation and bootstrap replication, the sign would often change from positive to

negative.

The worldwide collaboration that enabled this study and the detailed clinical data reported

by physicians or trained medical staff is an important strength of this study. The machine

learning approach allowed us to consider a wide variety of potential associations with

adverse outcomes, and we examined multiple adverse COVID-19-related adverse outcomes

enabling preliminary comparisons between risks. Certain comorbidities, including COPD,

CVD, and cancer, were not as strongly associated with Hospitalization+ as they were for

death. In contrast, severe IBD disease activity was an important predictor of

Hospitalization+ but was not consistently associated with a higher risk of ICU+ or death.

Limitations

The data for this study comes from a voluntary registry, and the sampling process is

unknown. Reported cases may underrepresent both low-risk asymptomatic cases and

severely ill patients who may be hospitalized at an outside hospital or die without their

healthcare provider's knowledge. Our results are associational, not causal — when using

the online risk calculator, healthcare providers should not use it to answer "what-if"

questions (e.g., how an individual's risk would change if they altered the medications they

were taking) which are inherently causal questions[33]. While the registry has a wealth of

clinical data, it does not collect granular data on many social determinants of health.

Additionally, insurance status is not collected, which, for patients in the US, likely factors

into the decision making of whether to visit a hospital. Lastly, we cannot compare the risk

of adverse COVID-19 outcomes in IBD patients to that in the general population.

Conclusions

This prognostic model can effectively predict which IBD patients may be at higher risk for

COVID-19-related morbidity. The free and publicly available (https://covidibd.org/covid-

19-risk-calculator/) risk calculator should facilitate patient-provider discussions regarding

the individualized risk of COVID-19 based on patient and treatment-related factors. As

COVID-19 cases continue to rise in the US and the rest of the world, this tool will be

important in assisting physicians in identifying high-risk patients with downstream clinical

implications. This tool can inform public health efforts to promote rational vaccine

allocation and could help providers target their outreach to higher-risk patients. We

believe this approach can also serve as a model for risk stratification in other chronic

diseases.

Conflicts of Interest

John Sperger, Kushal S. Shah, Minxin Lu, Xian Zhang, Erica J. Brenner, Manasi Agrawal, and
Michael R. Kosorok report no conflicts of interest.

RCU has served as a consultant and/or advisory board member for Bristol Myers Squibb,
Eli Lilly, Janssen, Pfizer, and Takeda. He has received research support from AbbVie,
Boehringer Ingelheim, and Pfizer. He is supported by a Career Development Award from
the National Institutes of Health (K23KD111995-01A1).

JFC reports receiving research grants from AbbVie, Janssen Pharmaceuticals and Takeda;
receiving payment for lectures from AbbVie, Amgen, Allergan, Inc. Ferring Pharmaceuticals,
Shire, and Takeda; receiving consulting fees from AbbVie, Amgen, Arena Pharmaceuticals,
Boehringer Ingelheim, Celgene Corporation, Celltrion, Eli Lilly, Enterome, Ferring
Pharmaceuticals, Genentech, Janssen Pharmaceuticals, Landos, Ipsen, Medimmune, Merck,
Novartis, Pfizer, Shire, Takeda, Tigenix, Viela bio; and hold stock options in Intestinal
Biotech Development and Genfit.

References

1. Lloyd-Jones DM, Braun LT, Ndumele CE, et al. Use of Risk Assessment Tools to Guide Decision-Making in the Primary Prevention of Atherosclerotic Cardiovascular Disease: A Special Report From the American Heart Association and American College of Cardiology. *Circulation*. 2019;139(25). doi:10.1161/CIR.0000000000000638

2. Torres J, Mehandru S, Colombel J-F, Peyrin-Biroulet L. Crohn's disease. *The Lancet*. 2017;389(10080):1741-1755.

3. Ungaro R, Mehandru S, Allen PB, Peyrin-Biroulet L, Colombel J-F. Ulcerative colitis. *The Lancet*. 2017;389(10080):1756-1770. doi:10.1016/S0140-6736(16)32126-2

4. Tibshirani R. Regression shrinkage and selection via the lasso. *Journal of the Royal Statistical Society: Series B (Methodological)*. 1996;58(1):267-288.

5. World Health Organization. WHO Coronavirus Disease (COVID-19) Dashboard. Accessed November 1, 2020. https://covid19.who.int

6. Poblador-Plou B, Carmona-Pírez J, Ioakeim-Skoufa I, et al. Baseline chronic comorbidity and mortality in laboratory-confirmed COVID-19 cases: Results from the PRECOVID study in Spain. *International journal of environmental research and public health*. 2020;17(14):5171.

7. Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19-related death using OpenSAFELY. *Nature*. 2020;584(7821):430-436.

8. Dun C, Walsh C, Bae S, et al. A Machine Learning Study of 534,023 Medicare Beneficiaries with COVID-19: Implications for Personalized Risk Prediction. *medRxiv*. Published online 2020.

9. Jehi L, Ji X, Milinovich A, et al. Development and validation of a model for individualized prediction of hospitalization risk in 4,536 patients with COVID-19. *PloS one*. 2020;15(8):e0237419.

10. Fakhoury M, Negrulj R, Mooranian A, Al-Salami H. Inflammatory bowel disease: clinical aspects and treatments. *J Inflamm Res*. 2014;7:113-120. doi:10.2147/JIR.S65979

11. Lin SC, Cheifetz AS. The Use of Complementary and Alternative Medicine in Patients With Inflammatory Bowel Disease. *Gastroenterol Hepatol (N Y)*. 2018;14(7):415-425.

12. Moons KG, Altman DG, Reitsma JB, et al. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): explanation and elaboration. *Annals of internal medicine*. 2015;162(1):W1-W73.

13. Rubin DT, Abreu MT, Rai V, et al. Management of patients with Crohn's disease and ulcerative colitis during the coronavirus disease-2019 pandemic: results of an international meeting. *Gastroenterology*. 2020;159(1):6-13. e6.

14. Brenner EJ, Ungaro RC, Gearry RB, et al. Corticosteroids, But Not TNF Antagonists, Are Associated With Adverse COVID-19 Outcomes in Patients With Inflammatory Bowel Diseases: Results From an International Registry. *Gastroenterology*. 2020;159(2):481-491.e3. doi:10.1053/j.gastro.2020.05.032

15. Vandenbroucke JP, Von Elm E, Altman DG, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *PLoS Med*. 2007;4(10):e297.

16. Rubin DB. Multiple imputation after 18+ years. *Journal of the American statistical Association*. 1996;91(434):473-489.

17. van Buuren S, Groothuis-Oudshoorn K. mice: Multivariate imputation by chained equations in R. *Journal of statistical software*. Published online 2010:1-68.

18. Zou H, Hastie T. Regularization and variable selection via the elastic net. *Journal of the royal statistical society: series B (statistical methodology)*. 2005;67(2):301-320.

19. Hastie T, Tibshirani R, Wainwright M. *Statistical Learning with Sparsity: The Lasso and Generalizations*. CRC press; 2015.

20. Meier L, Van De Geer S, Bühlmann P. The group lasso for logistic regression. *Journal of the Royal Statistical Society: Series B (Statistical Methodology)*. 2008;70(1):53-71.

21. Simon N, Friedman J, Hastie T, Tibshirani R. A sparse-group lasso. *Journal of computational and graphical statistics*. 2013;22(2):231-245.

22. Efron B, Tibshirani R. Bootstrap methods for standard errors, confidence intervals, and other measures of statistical accuracy. *Statistical science*. Published online 1986:54-75.

23. Team RC. *R: A Language and Environment for Statistical Computing*. Vienna, Austria; 2013.

24. Wickham H, Averick M, Bryan J, et al. Welcome to the Tidyverse. *Journal of Open Source Software*. 2019;4(43):1686.

25. Friedman J, Hastie T, Tibshirani R. Regularization paths for generalized linear models via coordinate descent. *Journal of statistical software*. 2010;33(1):1.

26. Microsoft, Ooi H. *GlmnetUtils: Utilities for "Glmnet."*; 2020. Accessed December 4, 2020. https://CRAN.R-project.org/package=glmnetUtils

27. Milton Bache S, Wickham H, Henry L, RStudio. *Magrittr: A Forward-Pipe Operator for R*.; 2020. Accessed December 4, 2020. https://CRAN.R-project.org/package=magrittr

28. Bengtsson H. *Future: Unified Parallel and Distributed Processing in R for Everyone*.; 2020. Accessed November 5, 2020. https://CRAN.R-project.org/package=future

29. Robin X, Turck N, Hainard A, et al. *PROC: Display and Analyze ROC Curves*.; 2020. Accessed September 5, 2020. https://CRAN.R-project.org/package=pROC

30. Chang W, Cheng J, Allaire JJ, et al. *Shiny: Web Application Framework for R*.; 2020. Accessed December 5, 2020. https://CRAN.R-project.org/package=shiny

31. Kim L, Garg S, O'Halloran A, et al. Risk factors for intensive care unit admission and in-hospital mortality among hospitalized adults identified through the US coronavirus disease 2019 (COVID-19)-associated hospitalization surveillance network (COVID-NET). *Clinical Infectious Diseases*. Published online 2020.

32. Ungaro RC, Brenner EJ, Gearry RB, et al. Effect of IBD medications on COVID-19 outcomes: results from an international registry. *Gut*. Published online October 20, 2020. doi:10.1136/gutjnl-2020-322539

33. Hernán MA, Robins JM. Chapter 1 A Definition of Causal Effect. In: *Causal Inference: What If*. ; 2020:311.

Table 1. Main Characteristics of COVID-19 IBD Patients in the Study[a]

Characteristics	Training Data (n=2009)	Test Data (n=700)	Overall (n=2709)
Age, mean (SD), years	42.2 (18.2)	38.7 (17.4)	41.2 (18.0)
Gender, No. (%)			
Female	982 (48.9%)	344 (49.1%)	1326 (48.9%)
Male	998 (49.7%)	341 (48.7%)	1339 (49.4%)
Other	1 (0.0%)	0 (0.0%)	1 (0.0%)
Asian[b], No. (%)	112 (5.6%)	38 (5.4%)	150 (5.5%)
Black[b], No. (%)	138 (6.9%)	39 (5.6%)	177 (6.5%)
White[b], No. (%)	1603 (79.8%)	547 (78.1%)	2150 (79.4%)
Hispanic/Latino, No. (%)	350 (17.4%)	115 (16.4%)	465 (17.2%)
Missing	375 (18.7%)	120 (17.1%)	495 (18.3%)
BMI, mean (SD)	26.0 (6.50)	25.2 (6.26)	25.8 (6.44)
Missing	398 (19.8%)	106 (15.1%)	504 (18.6%)
Current smoker, No. (%)	61 (3.0%)	25 (3.6%)	86 (3.2%)
Disease type, No. (%)			
Crohn's disease	1115 (55.5%)	401 (57.3%)	1516 (56.0%)
Ulcerative colitis	854 (42.5%)	278 (39.7%)	1132 (41.8%)
Cardiovascular disease, No. (%)	133 (6.6%)	43 (6.1%)	176 (6.5%)
Diabetes, No. (%)	117 (5.8%)	30 (4.3%)	147 (5.4%)
Hypertension, No. (%)	243 (12.1%)	67 (9.6%)	310 (11.4%)
Count of comorbidities, mean (SD)	0.544 (0.938)	0.479 (0.879)	0.527 (0.923)
Biologic therapy, No. (%)	1203 (59.9%)	437 (62.4%)	1640 (60.5%)
Tumor Necrosis Factor inhibitor, No. (%)	796 (39.6%)	313 (44.7%)	1109 (40.9%)
Anti-integrin, No. (%)	213 (10.6%)	72 (10.3%)	285 (10.5%)
IL 12/23 inhibitor, No. (%)	187 (9.3%)	47 (6.7%)	234 (8.6%)
5-Aminosalicylates, No. (%)	636 (31.7%)	200 (28.6%)	836 (30.9%)
Sulfasalazine, No. (%)	64 (3.2%)	24 (3.4%)	88 (3.2%)
Mesalamine, No. (%)	561 (27.9%)	175 (25.0%)	736 (27.2%)
Immunomodulators, No. (%)	459 (22.8%)	140 (20.0%)	599 (22.1%)
Methotrexate, No. (%)	81 (4.0%)	24 (3.4%)	105 (3.9%)
Azathioprine or 6-Mercaptopurine, No. (%)	367 (18.3%)	110 (15.7%)	477 (17.6%)
Corticosteroids, No. (%)	209 (10.4%)	65 (9.3%)	274 (10.1%)
Budesonide, No. (%)	59 (2.9%)	17 (2.4%)	76 (2.8%)
Oral or parenteral steroids, No. (%)	154 (7.7%)	49 (7.0%)	203 (7.5%)
Janus kinase inhibitors (tofacitinib), No. (%)	30 (1.5%)	9 (1.3%)	39 (1.4%)
Hospitalization+, No. (%)	499 (24.8%)	138 (19.7%)	637 (23.5%)
Missing	37 (1.8%)	17 (2.4%)	54 (2.0%)
ICU+, No. (%)	133 (6.6%)	36 (5.1%)	169 (6.2%)
Missing	49 (2.4%)	22 (3.1%)	71 (2.6%)
Death, No. (%)	57 (2.8%)	12 (1.7%)	69 (2.5%)
Missing	33 (1.6%)	14 (2.0%)	47 (1.7%)

[a]Missingness is only reported for predictors with >5% missing values, and for all outcomes. Only comorbidities with an overall prevalence above 5% are shown in this table. For a complete list of characteristics and number and percentage of missing values, see supplement eTable 2.
[b]Individuals can be assigned to more than one physician-reported racial group (White, Black, Asian).
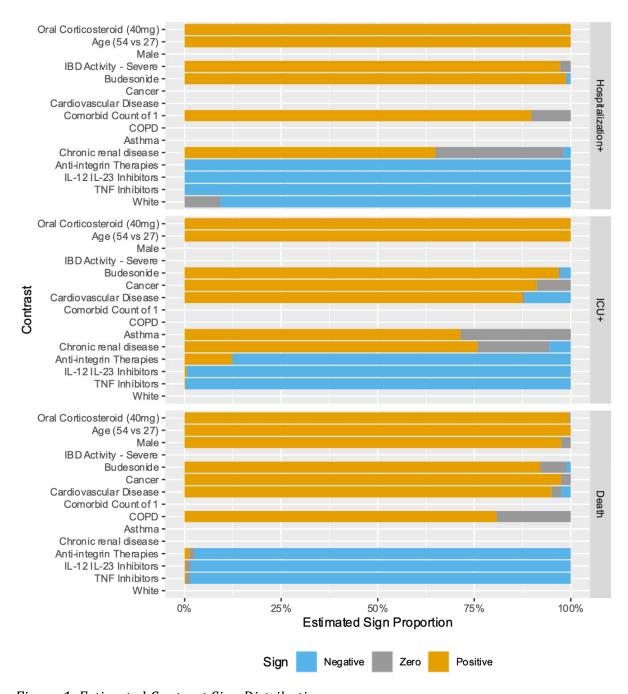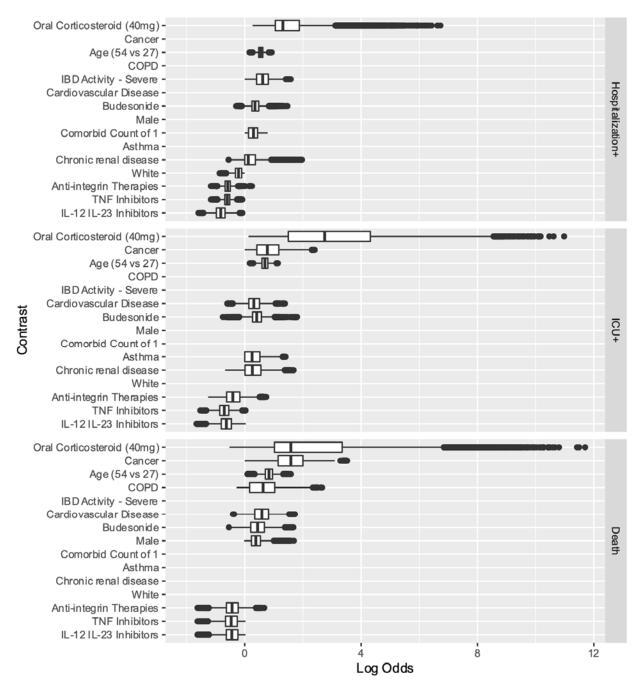
Figure 1: Estimated Contrast Sign Distribution

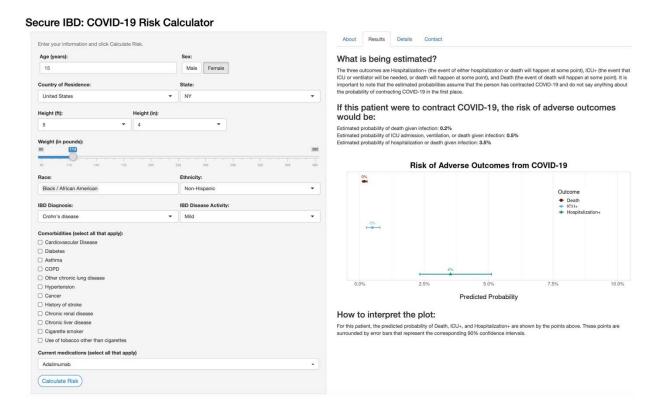*Figure 2: Estimated Contrast Effect Size Distribution*

Figure 3A - An example patient with below-average predicted risk. Young age, gender, and a lack of comorbidities contribute to a lower-than-average risk of adverse COVID-19 outcomes.
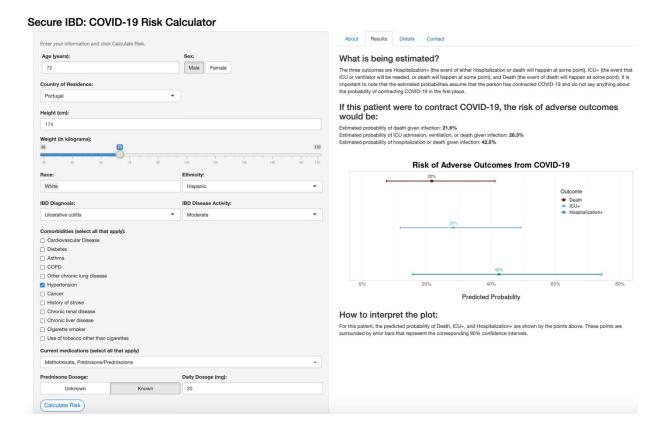
Figure 3B - An example patient with above-average predicted risk. Older age, prednisone dosage, and hypertension were the major contributors to increased risk, with ethnicity having a small positive association with increased risk.

Figure 3: Online Risk Prediction Tool. The data entry and results for two example patients are depicted.