Leveraging near-real-time patient and population data to incorporate fluctuating risk of severe COVID-19: development and prospective validation of a personalised risk prediction tool

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Summary

Background Novel strategies that account for population-level changes in dominant variants, immunity, testing practices and changes in individual risk profiles are needed to identify patients who remain at high risk of severe COVID-19. The aim of this study was to develop and prospectively validate a tool to predict absolute risk of severe COVID-19 incorporating dynamic parameters at the patient and population levels that could be used to inform clinical care.

Methods A retrospective cohort of vaccinated US Veterans with SARS-CoV-2 from July 1, 2021, through August 25, 2023 was created. Models were estimated using logistic-regression-based machine learning with backward selection and included a variable with fluctuating absolute risk of severe COVID-19 to account for temporal changes. Age, sex, vaccine type, fully boosted status, and prior infection before vaccination were included *a priori*. Variations in individual risk over time, e.g., due to receipt of immune suppressive medications, were also potentially included. The model was developed using data from July 1, 2021, through August 31, 2022 and prospectively validated on a subsequent second cohort (September 1, 2022, through August 25, 2023). Model performance was quantified by the area under the receiver operating characteristic curve (AUC) and calibration by Brier score. The final model was used to compare observed rates of severe disease to predicted rates among patients who received oral antivirals.

Findings 216,890 SARS-CoV-2 infections in Veterans not treated with oral antivirals were included (median age, 65; 88% male). The development cohort included 165,303 patients (66,121 in the training set, 49,591 in the tuning set, and 49,591 in the testing set) and the prospective validation cohort included 51,587 patients. The percentage of severe infections ranged from 5% to 25%. Model performance improved until 24 clinical predictor variables including age, co-morbidities, and immune-suppressive medications plus a 30-day rolling risk window were included (AUC in development cohort, 0.88 (95% CI, 0.87–0.88), AUC in prospective validation, 0.85 (95% CI, 0.84–0.85), Brier Score, 0.13). The most important variables for predicting severe disease included age, chronic kidney disease, chronic obstructive pulmonary disease, Alzheimer's disease, heart failure, and anaemia. Glucocorticoid use during the one-month prior to COVID-19 diagnosis was the next most important predictor. Models that included a near-real time fluctuating population risk variable performed better than models stratified by circulating variant and models with dominant variant included as a predictor. Patients with predicted severe disease risk >3% who received oral antivirals had approximately 4-fold lower rates of severe COVID-19 untreated patients at a similar risk level.

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Interpretation Our novel risk prediction tool uses a simple method to adjust for temporal changes and can be implemented to facilitate uptake of evidence-based therapies. The study provides proof-of-concept for leveraging real-time data to support risk prediction that incorporates changing population-level trends and variation patient-level risk.

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Keywords: COVID-19; SARS-CoV-2; Risk prediction; Clinical decompensation scores; Learning health systems; Dynamic sustainability; Clinical informatics

Research in context

Evidence before this study

We searched PubMed database, from database inception to January 10, 2024, with no language restrictions, initially using the terms "COVID severity prediction." This search yielded over 11,000 results. Adding "model" reduced to over 4000 results. We therefore added "systematic review," which yielded 94 results, and chose the most recent review of studies that used multivariable modeling in large databases. Immunity has greatly reduced the incidence of severe COVID-19. Antivirals and additional vaccine doses can reduce risk in some populations, but do not improve outcomes in lower risk populations.

Added value of this study

Risk prediction tools based on a combination of patient-level risk factors and dynamic disease risk can be leveraged to support personalised approaches to management of severe COVID-19. The risk prediction tool developed and prospectively validated in this study has the potential to support outreach efforts to those who remain at risk of severe COVID-19 for distribution of antivirals and additional doses of vaccines.

Implications of all the available evidence

Vaccination has greatly reduced the risk of severe COVID-19, however, some patients continue to develop severe outcomes. Antivirals reduce risk in high-risk populations only. Personalised risk prediction tools may be a strategy for improving uptake and distribution of evidence-based therapies to individuals who will derive benefit from these approaches.

Introduction

The ideal of the Learning Health System model is that data generated in near-real time can be used to guide clinical decision-making.[1,2] Clinical medicine is rapidly changing, presenting challenges and opportunities. Ideally, approaches that account for changes in health status at the level of the individual and also changing epidemiologic conditions at the population level can be developed to improve and personalise clinical decision-making.

The host–pathogen interaction is inherently dynamic—as humans develop strategies to combat infections, infectious agents evolve to evade them.[3] First generation mRNA vaccines were highly effective in preventing infections against the ancestral strain of SARS-CoV-2 but drove viral evolution and the predominance of different variants. Viral evolution and immune evasion led to the omicron wave, which resulted in widespread population immunity. These changes—in immunity, therapeutics, and circulating variants—resulted in longitudinal changes in risk of severe COVID-19 disease.[4–8] Because of this progress, static prediction tools developed during the early phases of the pandemic that do not account for fluctuations in disease severity may no longer be relevant, due to reliance on retrospective data collected prior to widespread immunity, a focus on specific time periods,[9] and/or risk of clinical decompensation after admission rather than uptake of interventions to prevent disease progress.[10,11] Novel informatics strategies that leverage contemporaneous data are needed to address the perennial challenge of longitudinal change.

Despite medical advances, some patients remain at risk for severe COVID-19 despite vaccination; risk factors include age, advanced heart, lung and kidney disease, and receipt of immune-suppressive medications.[12–14] Some of these risk factors, such as receipt of immune suppressive medications, are time-varying at the level of the individual patient, such that a patient can be exposed or unexposed at different time points. Patients who remain at high risk of severe disease would benefit from available interventions, such as early receipt of antiviral medications or frequent boosting.[15–17]

Pursuit of these medical interventions has been limited for several reasons,[18] creating a need for implementation strategies to improve uptake. In theory, risk prediction tools could be used by clinicians and patients to identify those who remain at substantial risk of severe

disease and to inform outreach activities for booster vaccination and early antiviral treatment.[18] Novel informatics solutions that integrate dynamic risk levels are needed maintain the relevance of tools for improving care. Thus, the aim of this study was to leverage near-real-time data from nationwide electronic medical records from patients in the Veterans Health Administration (VA) to develop, validate, and test a personalised and dynamic risk prediction tool for estimating absolute risk of severe COVID-19.

Methods

Data sources, participants, and study design

Data were obtained from the VA COVID-19 Shared Data Resource[19] and the Corporate Data Warehouse (CDW), which collates electronic health record (EHR) data from VA facilities nationwide. All vaccinated Veteran patients who subsequently developed SARS-CoV-2 during two time periods were included: July 1, 2021–August 31, 2022 (Development Era) and September 1, 2022–August 25, 2023 (Prospective Validation Era). Given the aim to develop a tool for predicting risk of severe COVID-19 in the absence of treatment, patients treated with nirmatrelvir/ritonavir (Paxlovid) or molnupiravir (Lagevrio) were excluded. The final model was then applied to the larger cohort, which included Veteran patients who did and did not receive these antivirals, so that predicted and observed rates of severe COVID-19 could be calculated among treated and untreated patients.

Outcome

Severe breakthrough COVID-19 was defined as in our previously published work.[8,13] In brief, severe cases included any death between 2 and 28 days after a positive SARS-CoV-2 test and/or hospitalisation within 14 days of the positive test with documented SpO2 <94%, receipt of supplemental oxygen, use of dexamethasone, or mechanical ventilation. Death could not be attributed to COVID-19 versus other causes, since data from death certificates are not available for most VA patients and when present appear as scanned documents rather than as structured data.

Patient-level predictors and potential risk factors

Candidate predictors of severe disease were based on published literature and included age, sex, race, ethnicity, region, vaccine type, prior SARS-CoV-2 infection, body mass index, receipt of at least one additional vaccine dose (booster), treatment with immune-suppressive drugs (chemotherapy, cytokine blockers, glucocorticoids, leukocyte inhibitors, and/or lymphocyte depleting drugs) before infection, and 30 separate comorbidities defined per the Chronic Conditions Warehouse (CCW). See sTable 1 for definitions of all data elements.

Immune suppressive medication variables were defined based on documented administrations (intravenous medications) and/or dispenses (oral medications) during a pre-specified window period at the time of the SARS-CoV-2 diagnosis. Thus, presence of the exposure for estimating risk of severe disease could vary longitudinally at the level of the individual patient. For example, if a patient received corticosteroids for a one-month period, their elevation in risk would last for the duration of receipt of the medication plus an additional 30 days. If they were diagnosed with SARS-CoV-2 during this window period, they would be considered to be exposed. After the end of the 30-day window, if the medication were discontinued, the patient would be considered unexposed to corticosteroids. Duration of the impact of the immune suppressive medication varied by drug and ranged from one month prior to SARS-CoV-2 diagnosis (glucocorticoids) to 18 months (lymphocyte-depleting medications, e.g., rituximab). Immune suppression from chemotherapy was estimated to last six months. All definitions are identical to those previously published except that comorbidities were ascertained using a 1-year period prior to the date of the breakthrough infection.

Population-level risk of severe disease

Baseline risk of severe COVID-19 disease at the population-level fluctuated widely over time. To account for this longitudinal variation, an additional predictor variable was created to quantify the proportion of recent COVID-19 cases that were severe. This "rolling risk" of severe COVID-19 was defined for each day of the study period as the empirical frequency of severe COVID-19 among breakthrough infections occurring during a 30-day window prior to that "index date." For cases occurring during the Development Era, to leverage the retrospective nature of the data and obtain the most accurate estimate of rolling risk on a given date, rolling risk was calculated without any lag between COVID diagnosis and outcome ascertainment. Specifically, the 30-day rolling risk of severe COVID-19 for 7/31 would include COVID-19 cases diagnosed between 7/1 and 7/30. However since severe COVID-19 is assessed based on data up to 28 days after the date of breakthrough infection (e.g., patients become infected and then subsequently develop a severe outcome 2–4 weeks later), for the purposes of assessing the utility of the tool in real-world settings, we added a 28-day lag between the index date and the window used to calculate rolling risk during the Prospective Validation Era. This is necessary to assess the feasibility of using the tool in clinical practice where it would be impossible to calculate rolling risk with a shorter lag period. In addition to a rolling risk variable, we also considered other mechanisms for incorporating dynamic changes in risk of severe disease, including stratification by dominant variant and inclusion of variant type as a predictor in the models.

Model development and selection

Prediction model development and refinement occurred in two stages. The first stage, the Development Era, was used for initial model development and internal validation. The Development Era dataset was randomly allocated to train, tune, and test sets for the initial model estimation. The items adjusted based on model performance in the Tune set included the definition of features, the selection of features to include, and the parameters involved in calculating the rolling risk of severe disease. During the second stage, after the model had been specified using retrospective data, the Prospective Validation Dataset was used to conduct a prospective validation.

Prediction model development was conducted entirely using data from the Development Era Train set. Model and variable selection were based on data from the Development Era Tune set. In preliminary analyses, we compared logistic regression to more complex machine learning methodologies (random forests, gradient boosting machines, multilayer perceptron). Five variables were included *a priori* in all models: age, sex, vaccine type, fully boosted status, and prior infection before vaccination. These variables were selected for two reasons: First, to ensure that the model could be programmed into a publicly-facing risk prediction calculator that could be used regardless of medical knowledge or expertise—information about age, sex, and immune status are generally knowable without access to more detailed medical data. Second, because they had been shown in multiple studies in diverse healthcare systems to be associated with risk of severe COVID-19. In a sensitivity analysis, a model in which these variables were not included *a priori* was tested. In models that adjusted for baseline population risk of severe disease, the risk variable (e.g. 30-day rolling risk, delta variant indicator) was also included *a priori*. An additional 36 variables were considered for possible inclusion using a backward selection approach using area under the receiver operating characteristic curve as the performance metric.

Most variables were categorical from the outset, e.g., presence or absence of a comorbidity or use or non-use of a class of immune-suppressive drug. Continuous variables, such as age, were cut into categorical variables *a priori* based on subject matter expertise. Categorical variables with more than two unique values were forced to be included or excluded as a group.

Power and sample size calculation

Using the method of Riley et al. and assuming a 10% rate of a severe outcome, the study would require a minimum of 6113 subjects to support development of a model with a maximum of 72 predictor variables.[20]

Model evaluation

Model performance was evaluated using measures of discrimination and calibration. The primary measure of discrimination was the area under the receiver operating characteristic curve (ROC AUC),[21,22] which measures how well predicted risks generated by the model discriminate between patients who did versus did not experience the event (severe versus non-severe COVID-19). Calibration was assessed by plotting the cumulative risk against mean predicted risks, within deciles of the predicted risk.[23] Different models (e.g., models with different numbers of variables and/or methods of modelling baseline risk of severe disease) were then compared using calibration plots and AUC, with AUC >0.8 indicating excellent predictive utility and Brier scores closest to zero indicating ideal model calibration.[24–26] The optimal model was selected based on these features and using considerations about feasibility and future-proofing. To ensure that models performed similarly cross different demographic groups, several models stratified by race, ethnicity, and sex were also evaluated.

All data were analysed using R version 4.2.1 and Python version 3.8.5.

Potential impact of antivirals as assessed by the risk prediction tool

Breakpoints of 1%, 3%, 5%, 10%, and 20% of predicted risk of severe COVID-19 in the event of breakthrough infection and absence of antiviral treatment were used in two ways: 1) as thresholds (>1%, >3%, >5%) or 2) as intervals (<1%, 1–3%, 3–5%, 5–10%, 10–20%, >20%). The numbers of severe and total cases were used to calculate incidence of severe COVID-19 among patients with SARS-CoV-2 infection, stratified by use or non-use of an oral antiviral. In the primary analysis, the data in the treated group were interpreted as the incidence of progression to severe disease among patients evaluated and treated during mild-to-moderate disease.

Secondary analysis of potential impact

In a secondary approach to estimating the potential impact of the tool for reducing severe disease, the numbers of severe cases that represented progression to severe disease were re-estimated in both groups based on chart review of cases identified as severe by algorithm in a previously published study.[27] These re-estimated data were used to calculate the absolute difference in incidence between untreated and treated patients, with NNT calculated as 1 divided by that difference.

Chart review for secondary analysis of antiviral use and utility

Among patients with solid organ transplantation, chronic lymphocytic leukemia, or plasma cell malignancies whose charts were reviewed to identify patients who had not received antiviral drugs between March 1, 2022, and September 30, 2022,[27] cases classified as severe by the electronic algorithm above were reviewed (by

P.A.M.) and re-classified as either: 1) non-severe infection, which could represent either hospitalisation for COVID-19 not regarded as severe by the providers or severe illness not thought to be attributable to or influenced by SARS-CoV-2 infection; 2) infection already severe at the time of initial evaluation; or 3) severe infection representing progression from infection that was non-severe at initial evaluation.

The percentages resulting from this review were then applied to the large datasets in the current study. First, the proportion of cases that truly represented severe COVID-19 was calculated among patients treated or untreated with oral antiviral drugs. Second, the expected proportion of true severe cases that were severe at initial evaluation was subtracted only in the group not treated with antivirals, since they would have been ineligible for treatment. It was assumed that antiviral treatment was given appropriately, i.e. only to patients with mild-to-moderate disease. It was further assumed that results of re-classification of "severe" cases by chart review of patients with the 3 specific high-risk conditions above would be generalizable across all levels of risk, with or without use of oral antivirals.

Ethical considerations

This study was approved as exempt human subjects research with a waiver of consent by the VA Boston Research and Development Committee prior to data collection and analysis (Study approval number, 3328-X).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Patient characteristics

Among 4,496,260 vaccinated Veterans, 255,251 breakthrough infections were identified, including 216,890 in Veterans not treated with oral antivirals (Fig. 1). The Development Era (7/1/2021 through 8/31/2023) included 165,303 infections, further randomly subdivided into a train set (66,121, 40%), tune set (49,591, 30%), and test set (49,591, 30%), and the Prospective Validation Era (9/1/2022–8/25/2023) included 51,587 infections.

Cohort characteristics are summarised in Table 1. The median age was 65. Patients were predominantly male (88%), white (64%), and not Hispanic or Latino (84%), with substantial minority representation (25% Black or African American, 11% Hispanic or Latino), and were evenly distributed across US regions. During

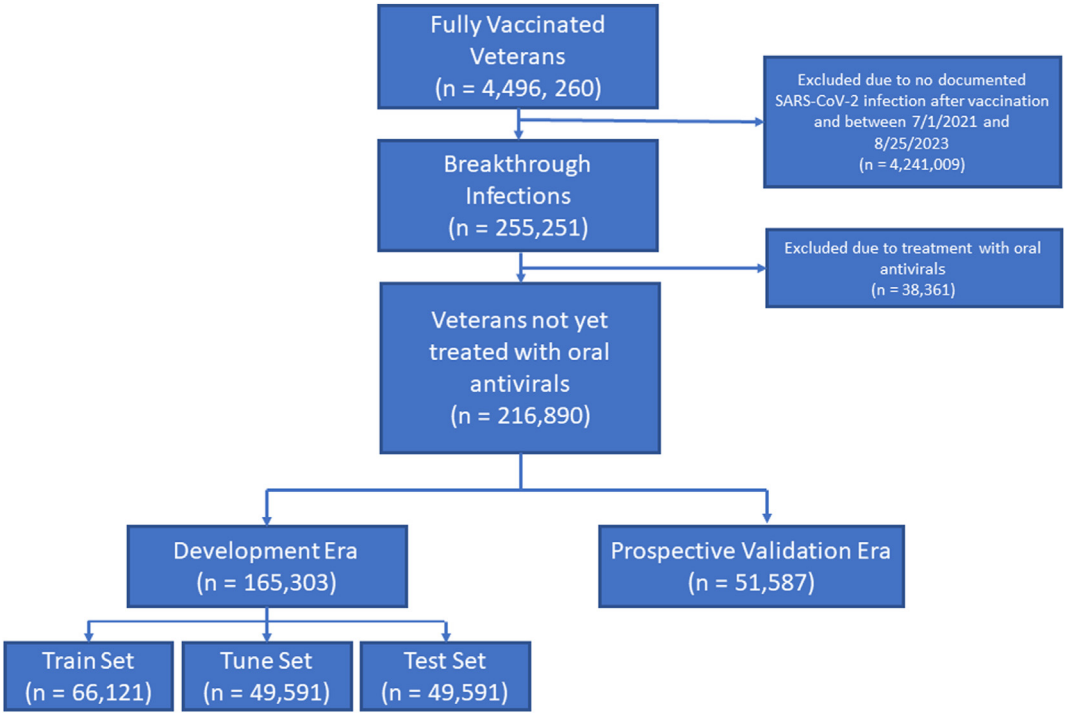

***Fig. 1:* Cohort flow diagram**. Patient flow diagram for inclusion criteria. Development era = July 1, 2021, through August 31, 2022, with patients randomly assigned to the train, tune, and test sets. Prospective Validation era = September 1, 2022 through August 25, 2023. Note that these time periods do not correspond to the appearance or disappearance of specific variants. For the purposes of model development, patients treated with antiviral medications were excluded.

Severe disease	Development era (July 1, 2021–August 31, 2022)		Prospective validation era (September 1, 2022–August 25, 3023)		Overall
	No	Yes	No	Yes	
Overall					
N (%)	149,523 (90%)	15,780 (10%)	43,222 (84%)	8365 (16%)	216,890
Age group					
<40	19,805 (13%)	182 (1%)	3589 (8%)	61 (1%)	23,637 (11%)
40–45	9173 (6%)	125 (1%)	1925 (4%)	41 (0%)	11,264 (5%)
45–50	9116 (6%)	179 (1%)	1917 (4%)	58 (1%)	11,270 (5%)
50–55	13,697 (9%)	395 (3%)	2896 (7%)	136 (2%)	17,124 (8%)
55–60	15,221 (10%)	704 (4%)	3741 (9%)	251 (3%)	19,917 (9%)
60–65	17,843 (12%)	1261 (8%)	5039 (12%)	531 (6%)	24,674 (11%)
65–70	16,333 (11%)	1911 (12%)	5184 (12%)	887 (11%)	24,315 (11%)
70–75	22,678 (15%)	3728 (24%)	7052 (16%)	1673 (20%)	35,131 (16%)
75–80	15,275 (10%)	3107 (20%)	6846 (16%)	2076 (25%)	27,304 (13%)
≥ 80	10,382 (7%)	4188 (27%)	5033 (12%)	2651 (32%)	22,254 (10%)
Gender					
Male	129,698 (87%)	15,159 (96%)	38,034 (88%)	8066 (96%)	190,957 (88%)
Race					
White	93,231 (62%)	11,387 (72%)	27,014 (63%)	6304 (75%)	137,936 (64%)
Black or African American	37,596 (25%)	3094 (20%)	11,103 (26%)	1381 (17%)	53,174 (25%)
American Indian or Alaska Native	1184 (1%)	130 (1%)	327 (1%)	56 (1%)	1697 (1%)
Asian	2555 (2%)	85 (1%)	625 (1%)	48 (1%)	3313 (2%)
Native Hawaiian or Other Pacific Islander	1582 (1%)	114 (1%)	412 (1%)	50 (1%)	2158 (1%)
Unknown	13,375 (9%)	970 (6%)	3741 (9%)	526 (6%)	18,612 (9%)
Ethnicity					
Hispanic or Latino	17,422 (12%)	1194 (8%)	5082 (12%)	716 (9%)	24,414 (11%)
Not Hispanic or Latino	124,622 (83%)	13,999 (89%)	36,018 (83%)	7301 (87%)	181,940 (84%)
Unknown	7479 (5%)	587 (4%)	2122 (5%)	348 (4%)	10,536 (5%)
Region					
Continental	24,286 (16%)	2644 (17%)	6888 (16%)	1273 (15%)	35,091 (16%)
Midwest	27,430 (18%)	3326 (21%)	8313 (19%)	1806 (22%)	40,875 (19%)
North Atlantic	31,980 (21%)	3294 (21%)	10,319 (24%)	1822 (22%)	47,415 (22%)
Pacific	28,799 (19%)	2702 (17%)	7796 (18%)	1543 (18%)	40,840 (19%)
Southeast	35,361 (24%)	3788 (24%)	9368 (22%)	1903 (23%)	50,420 (23%)
Unknown	1667 (1%)	26 (0%)	538 (1%)	18 (0%)	2249 (1%)
Vaccine type					
Moderna	63,517 (42%)	6712 (43%)	20,620 (48%)	4084 (49%)	94,933 (44%)
Pfizer	72,203 (48%)	7679 (49%)	19,772 (46%)	3828 (46%)	103,482 (48%)
Janssen	13,803 (9%)	1389 (9%)	2830 (7%)	453 (5%)	18,475 (9%)
Prior COVID infection					
Yes	5479 (4%)	437 (3%)	2093 (5%)	314 (4%)	8323 (4%)
BMI category					
Underweight	466 (0%)	223 (1%)	165 (0%)	124 (1%)	978 (0%)
Normal	16,374 (11%)	2868 (18%)	5312 (12%)	1551 (19%)	26,105 (12%)
Obesity I	43,748 (29%)	3936 (25%)	12,226 (28%)	2005 (24%)	61,915 (29%)
Obesity II	23,236 (16%)	2214 (14%)	6116 (14%)	1086 (13%)	32,652 (15%)
Overweight	44,755 (30%)	4581 (29%)	13,245 (31%)	2597 (31%)	65,178 (30%)
Extreme obesity	13,625 (9%)	1614 (10%)	3546 (8%)	719 (9%)	19,504 (9%)
Unknown	7319 (5%)	344 (2%)	2612 (6%)	283 (3%)	10,558 (5%)
Fully boosted					
Yes	63,579 (43%)	5934 (38%)	31,742 (73%)	6380 (76%)	107,635 (50%)
Immune-suppressive medications after vaccination					
Chemotherapy	1008 (1%)	488 (3%)	393 (1%)	275 (3%)	2164 (1%)

(Table 1 continues on next page)

Severe disease	Development era (July 1, 2021–August 31, 2022)		Prospective validation era (September 1, 2022–August 25, 3023)		Overall
	No	Yes	No	Yes	
(Continued from previous page)					
Cytokine blocking drugs	1976 (1%)	269 (2%)	549 (1%)	142 (2%)	2936 (1%)
Glucocorticoids	8542 (6%)	2637 (17%)	3264 (8%)	1501 (18%)	15,944 (7%)
Leukocyte inhibitory drugs	2069 (1%)	614 (4%)	624 (1%)	220 (3%)	3527 (2%)
Lymphocyte depleting drugs	601 (0%)	279 (2%)	178 (0%)	124 (1%)	1182 (1%)
Comorbidities					
Acquired hypothyroidism	11,774 (8%)	2533 (16%)	4102 (9%)	1376 (16%)	19,785 (9%)
Acute myocardial infarction	2107 (1%)	1556 (10%)	965 (2%)	891 (11%)	5519 (3%)
Alzheimer's disease	6200 (4%)	4109 (26%)	2949 (7%)	2420 (29%)	15,678 (7%)
Atrial fibrillation	11,282 (8%)	4410 (28%)	4661 (11%)	2513 (30%)	22,866 (11%)
Anaemia	19,683 (13%)	6944 (44%)	7572 (18%)	4022 (48%)	38,221 (18%)
Anxiety disorders	53,734 (36%)	5176 (33%)	15,575 (36%)	2825 (34%)	77,310 (36%)
Asthma	9330 (6%)	1050 (7%)	2831 (7%)	570 (7%)	13,781 (6%)
Bipolar disorder	13,349 (9%)	1811 (11%)	3873 (9%)	964 (12%)	19,997 (9%)
Chronic kidney disease	25,176 (17%)	9045 (57%)	9504 (22%)	4840 (58%)	48,565 (22%)
Colorectal cancer	1365 (1%)	429 (3%)	513 (1%)	245 (3%)	2552 (1%)
Chronic obstructive pulmonary disease	16,644 (11%)	6231 (39%)	6236 (14%)	3415 (41%)	32,526 (15%)
Depression	46,244 (31%)	5282 (33%)	12,721 (29%)	2537 (30%)	66,784 (31%)
Diabetes	44,160 (30%)	8267 (52%)	14,788 (34%)	4246 (51%)	71,461 (33%)
Epilepsy	2451 (2%)	797 (5%)	952 (2%)	461 (6%)	4661 (2%)
Heart failure	9845 (7%)	5258 (33%)	4226 (10%)	2987 (36%)	22,316 (10%)
HIV or AIDS	1516 (1%)	147 (1%)	388 (1%)	73 (1%)	2124 (1%)
Hyperlipidemia	77,490 (52%)	11,471 (73%)	25,037 (58%)	6315 (75%)	120,313 (55%)
Hypertension	81,997 (55%)	13,433 (85%)	27,145 (63%)	7206 (86%)	129,781 (60%)
Ischemic heart disease	23,473 (16%)	6905 (44%)	8849 (20%)	3880 (46%)	43,107 (20%)
Leukemias and Lymphomas	2181 (1%)	758 (5%)	797 (2%)	380 (5%)	4116 (2%)
Liver diseases	10,082 (7%)	2062 (13%)	3408 (8%)	1099 (13%)	16,651 (8%)
Lung cancer	1444 (1%)	787 (5%)	599 (1%)	478 (6%)	3308 (2%)
Mobility impairments	1996 (1%)	1143 (7%)	900 (2%)	703 (8%)	4742 (2%)
Multiple sclerosis	649 (0%)	172 (1%)	190 (0%)	81 (1%)	1092 (1%)
Peripheral vascular disease	7303 (5%)	2876 (18%)	3161 (7%)	1729 (21%)	15,069 (7%)
Pressure and chronic ulcers	2945 (2%)	2084 (13%)	1413 (3%)	1265 (15%)	7707 (4%)
Prostate cancer	8626 (6%)	1687 (11%)	3266 (8%)	1022 (12%)	14,601 (7%)
Schizophrenia	4940 (3%)	975 (6%)	1870 (4%)	524 (6%)	8309 (4%)
Tobacco use	21,602 (14%)	3794 (24%)	7119 (16%)	2112 (25%)	34,627 (16%)
Viral Hepatitis	3328 (2%)	806 (5%)	1110 (3%)	365 (4%)	5609 (3%)

Table 1: **Participant characteristics.**

the Development Era, 42% had received an additional vaccine dose at the time of the breakthrough infection, while 74% had received additional vaccine doses during the Prospective Validation Era. Among patients who experienced severe outcomes, comorbidities and receipt of immunosuppressive medications were common. Patient characteristics across the train, tune, and test sets within the development era were statistically similar (sTable 2).

The absolute risk of severe COVID-19 fluctuated substantially over the study period, ranging from 5% to nearly 25% of diagnosed infections, corresponding to time periods with different variants but also fluctuating immunity levels and testing density (Fig. 2). The number of infections and severe outcomes used to calculate the rolling risk also varied longitudinally (sFigures 1 and 2). During the full study period, 3002 patients died within 28 days of infection, representing 12% of the 24,145 cases classified as severe COVID-19, which was similar in the Development (13%) and Prospective Validation (11%) eras. An additional 674 deaths occurred 28–60 days after infection, representing only 0.3% of the cases classified as non-severe.

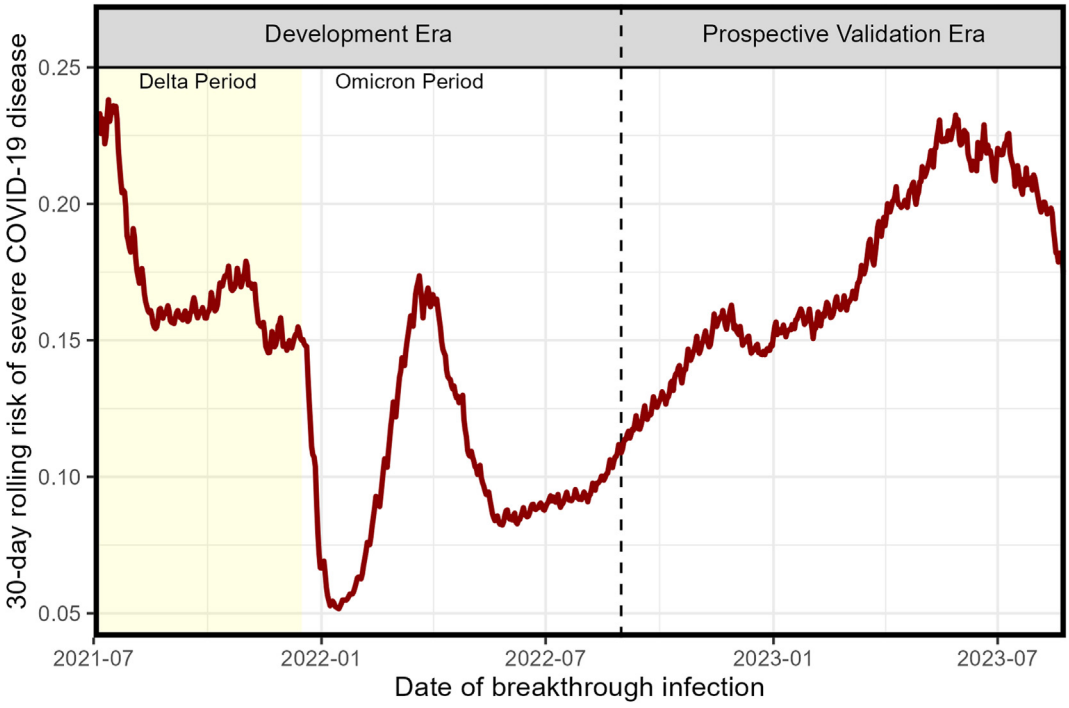

Fig. 2: **Longitudinal rolling risk of severe COVID-19**. Rolling risk of severe COVID-19 outcome in development and prospective validation eras. The y-axis refers to the proportion of all diagnosed breakthrough infections that met criteria for severe disease. A rolling risk window of 30 days is indicated in red, 90 days in burgundy, and 180 days in purple. Timing of the different development and validation eras is designated using vertical dotted lines.

Model development and selection

sFigure 3 shows the logistic-regression-based prediction model discrimination (AUC) and calibration (Brier score) in the Development Era tune set for models including between 6 and 42 clinical variables potentially predictive of risk of progression to severe disease. Performance increased monotonically with the number of variables included in the model, though with diminishing improvements as additional predictors were added.

Patient-level predictors

The most important potentially included risk factors in descending order of importance for predicting severe COVID-19 disease were chronic kidney disease, chronic obstructive pulmonary disease, Alzheimer's disease, heart failure, anaemia, and receipt of glucocorticoids within the one-month period prior to SARS-CoV-2 diagnosis. Other time-varying patient level factors included in the final model included receipt of lymphocyte-depleting medications within the 18-months prior to diagnosis, diagnosis of acute myocardial infarction, and receipt of cytotoxic chemotherapy within the six months prior to diagnosis. Receipt of other classes of immune suppressive medications, such as cytokine-blocking agents, was not included in the final logistic regression-based model.

Of the variables selected *a priori* for inclusion, age, fully boosted status, and vaccine type were the most important. Prior infection before vaccination was moderately important, and sex was minimally important. When running backwards selection without forcing in the variables selected *a priori*, age, fully boosted status, and vaccine type were all ranked in the top 25 most important predictors of severe disease (sTable 3), while prior infection before vaccination was ranked 26th and sex was ranked 34th.

Predictive performance was similar when other types of machine learning models were estimated (sTable 4), although the ranking of some of the variables was different with the different approaches. Chronic kidney disease and chronic obstructive pulmonary disease were the two most important risk factors across all model types. Glucocorticoid receipt was consistently selected, but receipt of lymphocyte-depleting medications was not. The other major differences included the relative importance of the geographic region variable, body mass index, and psychiatric disorders (depression, anxiety, schizophrenia).

Population-level predictors

Different methods for predicting risk of severe COVID-19 yielded similar performance, including adjustment by 30-day rolling risk of severe disease with adjustment by delta versus omicron periods, and stratification by delta versus omicron variant predominant periods. Ranking of the predictive utility of different clinical variables were consistent across different methods used to estimate the temporal baseline risk of severe outcome (sTable 3). Based on these findings, the final model included 24 clinical variables plus the 30-day rolling risk variable to estimate rolling risk of severe disease (Fig. 3). Model coefficients (estimated on the Development Era Train set) for the optimal model are presented in sTable 5.

Model validation

Discrimination (AUC) and calibration (Brier score) of the selected models in the development era test set, the first validation era, and the second validation era are shown in Fig. 4. AUC was excellent across both eras (Development, AUC of 0.88; Prospective Validation,

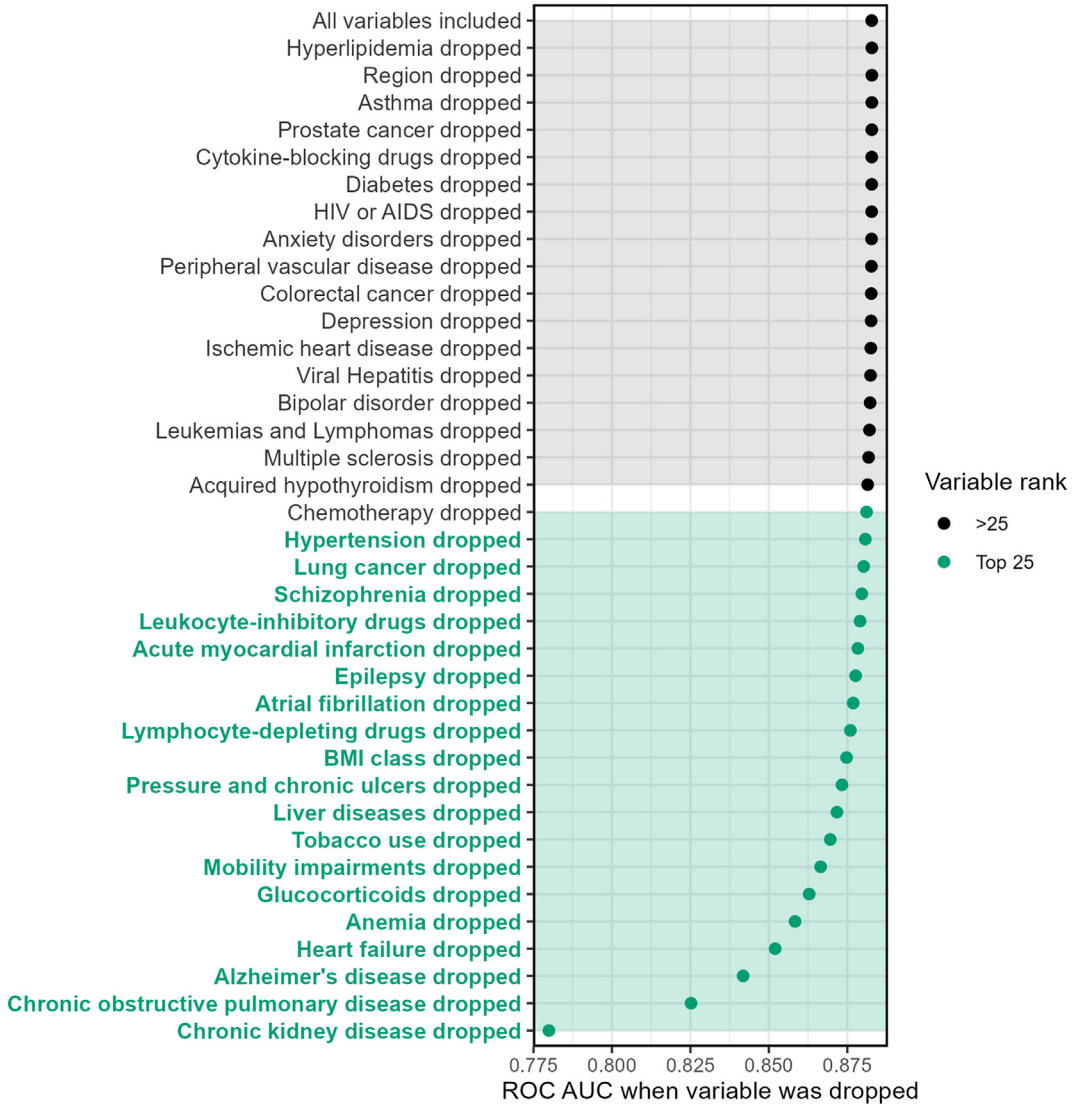

Fig. 3: **Prediction model variable selection**. Results of backward variable selection in the development era tune set adjusting by 30-day rolling risk of severe outcome. Variables with the least predictive value for estimating risk of severe disease are listed at the top of the plot and the most important variables are at the bottom. Each line of the plot represents the performance of the model when that variable (and any variable listed above it) was dropped from the model. The green box includes models fit with the top 25 variables. The top 25 variables include the 19 variables written in green text, as well as the six variables that were always included in the models (age, sex, vaccine type, receipt of a third vaccine dose, prior infection before vaccination, and 30-day rolling risk of severe outcome). If the variable was categorical, if one category was selected as a predictor, then all categories were included in the model. ROC AUC, area under the receiver operating characteristic curve.

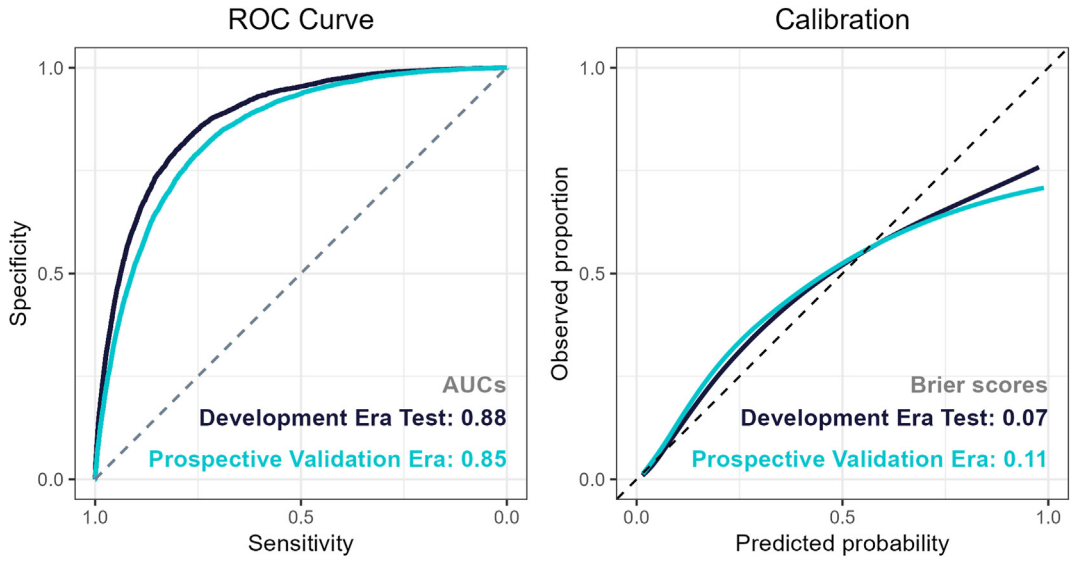

Fig. 4: **Prediction model performance and calibration plots**. Receiver operating characteristic (ROC) curves and calibration plots in the development era test set, first validation era, and second validation era for the optimal model with 25 variables. AUC, area under the ROC curve. Brier scores are a test of model calibration for observed versus predicted scores; values closer to zero indicate improved performance.

0.85). Calibration was also generally strong as indicated by the Brier scores, particularly in lower ranges of absolute risk of severe disease.

Trustworthiness and subgroup performance

In the stratified analysis to ensure the model performed similarly across demographic subgroups, model discrimination was consistently strong across all subgroups, with AUC 0.86 in females and 0.81 in males, 0.86 in non-white patients and 0.81 in white patients, 0.83 in Hispanic patients and 0.82 in non-Hispanic patients (sFigure 4). Calibration as measured by Brier scores was also consistently excellent (0.06 in female patients versus 0.14 in males; 0.09 in non-white patients versus 0.15 in white patients, 0.11 in Hispanic patients versus 0.13 in non-Hispanic patients).

Severe COVID-19 in patients treated with oral antiviral drugs

Breakthrough infection was also identified in 38,361 vaccinated patients who were treated with oral antivirals. Infections were classified as severe in 24,145/216,890 (11.1%) untreated and 1144/38,361 (3.0%) treated patients. 3062 (1.4%) untreated and 125 (0.3%) treated patients died 2–28 days after the positive test. Demographic and clinical characteristics of treated and untreated patients, stratified by severity of COVID-19, are shown in sTable 6.

Severe COVID-19 in treated and untreated patients stratified by predicted risk

The numbers of patients with severe and non-severe infection, stratified by baseline risk as predicted by the model and by receipt or non-receipt of oral antiviral drugs, are shown in Table 2, using either a minimum cut-point for risk or in intervals of risk. Incidences of progression despite antiviral treatment were typically 4-fold lower than incidences of severe disease without treatment in different risk strata: 0.9% versus 3.8%, 2.1% versus 8.0%, 4.8% versus 18.3%, and 13.2% versus 43.8%. These numbers provide accurate data on risk of severe COVID-19 among untreated patients and risk of progression among patients treated during mild-to-moderate disease.

Accurately quantifying the potential benefit of early antiviral treatment for preventing disease progression requires removing patients with severe disease at initial assessment, since they would not have been eligible for antiviral treatment. Manual review of 79 cases of disease classified as severe algorithmically identified 37 (47%) that did not represent severe COVID-19 (13 asymptomatic patients screened during hospitalisation for other reasons (6 of whom received outpatient antiviral regimens due to high risk of progression), 4 patients with positive tests on routine screening that were regarded as residual from prior symptomatic disease, and 20 patients with mild symptomatic infection that did not progress (14 of whom were treated with outpatient antiviral regimens)). Of the 42 true severe cases, 26 (33% of the total and 62% of the true cases) initially presented with severe COVID-19. 16 (20% of the total and 38% of the true COVID-19 cases) presented with mild-to-moderate COVID-19 but progressed to severe disease. Adjusted estimated numbers of cases of severe disease that progressed from mild-to-moderate disease, stratified by baseline risk as predicted by the model and

Absolute risk threshold	Untreated			Treated		
	Severe cases	N at risk	Risk	Severe cases	N at risk	Risk
>0.01	24,040	187,079	0.129	1138	35,812	0.032
>0.03	23,174	123,382	0.188	1072	24,747	0.043
>0.05	22,039	93,207	0.236	1008	17,667	0.057
Absolute risk stratum	**Untreated**			**Treated**		
	Severe cases	N at risk	Risk	Severe cases	N at risk	Risk
<0.01	105	29,811	0.004	6	2549	0.002
(0.01–0.03)	866	63,697	0.014	66	11,065	0.006
(0.03–0.05)	1135	30,175	0.038	64	7080	0.009
(0.05–0.1)	2745	34,427	0.080	164	7997	0.021
(0.1–0.2)	4600	25,201	0.183	250	5176	0.048
≥0.2	14,694	33,579	0.438	594	4494	0.132

Treated = use of an oral antiviral drug, presumed to be during mild-to-moderate disease. Untreated = no documented use of an oral antiviral drug. In the top section, groups are defined by minimum threshold of predicted risk. In the bottom section, groups are defined by strata of predicted risk.

Table 2: **Proportions of patients meeting criteria for severe COVID-19 among vaccinated patients with different ranges of predicted risk using a tool containing 25 clinical and demographic variables.**

by receipt or non-receipt of oral antiviral drugs, are shown in sTable 7, using either a minimum cut-point for risk or in intervals of risk, with calculation of absolute risk differences and NNT. NNT was too large to determine among patients with baseline predicted absolute risk <3%, whereas at predicted risk >20%, NNT was 37. Using >3% predicted risk as a cut-off for targeting antiviral treatment, NNT was 67.

Discussion

In this multi-year cohort study of more than 200,000 SARS-CoV-2 infections in vaccinated Veterans, we developed and prospectively validated a tool for estimating risk of severe COVID-19 that accounts for longitudinal fluctuations in risk at the population level and also patient-level changes in risk due to changing medical conditions and exposure to immune suppression. As measured by AUC and Brier scores, the model had high predictive utility and was well-calibrated, underscoring its potential as a clinical tool to support vaccine and therapeutics outreach to patients that remain at high risk of severe disease despite preventative measures such as vaccine-derived immunity. This study provides a proof-of-concept for how a learning health system approach to risk prediction can be operationalised. The potential clinical utility was demonstrated by confirming an approximately 4-fold reduction in risk of severe COVID-19 with early use of oral antivirals among patients with predicted risk >3%.

The dynamic sustainability framework highlights the need to adapt interventions to fit different contexts and conditions to maximise effectiveness.[28] This COVID-19 risk prediction model, which integrates rolling, near-real-time data in the setting of a dynamic host–pathogen interaction, integrates these pandemic-defining principles. Further, although our study focuses on risk prediction for severe COVID-19, the principles of dynamic change and varying absolute risk to support infectious diseases surveillance activities and public health responses have implications beyond this specific clinical application.[2,28]

Numerous predictive models have been published, with the great majority of them focused on hospitalised patients, to use data early in hospitalisation to determine risk of death or critical illness.[29–32] Our data expands upon this work to provide clinicians with a continually adapting and evolving tool that can be used to identify patients who remain at high risk of severe outcomes. In addition to accounting for longitudinal changes in risk due to changes in circulating variant and testing density, our model also inherently adjusts for patient-level changes in risk. Our study, in which absolute risk is updated based on changing risks and near-real time estimates, can serve as a framework and proof-of-concept for estimating clinical risk in other settings to improve care. For example, identification of effective therapeutics and vaccinations greatly improved COVID-19 outcomes, such that absolute risk of severe disease fell substantially; risk among identified cases then increased after testing policies changed. Similarly, identification of effective cancer therapeutics has reduced the risk of recurrence and has prolonged life; risk estimates provided to patients using retrospective data collected before the introduction of effective therapeutics will inherently overestimate risk and may lead to unnecessary stress and potentially unnecessary treatments. Similar strategies of using contemporaneous data are needed to inform clinical decision making across a variety of medical specialties.

Severity of disease resulting from infection with SARS-CoV-2, including all variants identified so far, is highly variable. Risk factors for severe disease were identified early in the pandemic in immunologically

naïve patients exposed to the original strain. Efforts to do so must account for the most prevalent variants that have evolved so far and for the patient's SARS-CoV-2 immunologic status, as estimated imperfectly by vaccination status and/or a history of previous infection as well as ongoing risk factors for immune suppression. Immune suppression exists on a spectrum and is itself variable. Immune suppression is a well-established risk factor for severe disease.[13,15,33,34] However, there is also evidence that once immune suppressive treatments such as cytotoxic chemotherapy are discontinued, patients are able to mount effective immune responses and the increase in risk wanes over time.[35] By leveraging rich electronic health records data about medication exposure, we were able to incorporate these changes in severe disease risk at the patient level.

The pivotal randomised controlled trials of nirmatrelvir and molnupiravir were conducted in unvaccinated patients with at least one risk factor for severe COVID-19 during mid-to-late 2021. At least 9 observational studies that have used propensity scores to balance treatment groups have provided convincing evidence of more modest benefit for nirmatrelvir or molnupiravir in vaccinated high-risk patients in the omicron era (Table 3). Studies that required only 1 risk factor for severe COVID-19 found risk reductions and NNTs similar to what we observed using a cut-off of >3% or >5% predicted risk without treatment.

Estimating risk for severe disease remains one of the most important clinical goals, especially for advising individual patients and their providers, as it has implications for vaccine outreach efforts and medication distribution. Multiple studies are consistent with our findings that high-risk but not low-risk vaccinated patients continue to derive benefit from early antiviral treatment (Table 3).[16,36] However, despite the potential for available preventative and therapeutic interventions to improve outcomes and reduce severe disease, uptake remains low.[27] This prediction tool could be used in the future to support outreach efforts to ensure that the highest risk group receives these evidence-based vaccines and therapeutics. Recent data suggests that this targeted approach has the potential to greatly increase uptake in this high-risk group (Carey et al, unpublished data).

The risk prediction tool uses only structured variables available in most electronic health record systems and is therefore designed for rapid implementation into

First author	Drug(s)	Type	Dates enrolled	Country	% vaccinated	Population	Population stratification	Outcome	% outcome untreated	% outcome treated	Risk difference	NNT
Hammond	N	RCT	7/2021–12/2021	International	0%	≥1 RF		HD	7	0.8	−6.2	16
Jayk Bernal	M	RCT	5/2021–10/2021	International	0%	≥1 RF		HD	14.1	7.3	−6.8	15
Butler	M	RCT	12/2021–4/2022	UK	100%	>50 or ≥1 RF	>age 50 or <age 50	HD	0.8	0.8	0	NA
Gottlieb	R	RCT	9/2020–4/2021	US, Euro	0%	≥1 RF		HD	5.3	0.7	−4.6	22
Yan[a]	N	Obs TTE	4/2022–3/2023	US(VA)	84%	≥1 RF	Quartiles of risk, IC	HD	2.6	1.9	−0.7[a]	143
Bajema	MN	Obs TTE	1/2022–7/2022	US(VA)	82%	≥1 RF		HD	5.3 (M), 3.4 (N)	4.4 (M), 2.3 (N)	−0.9 (M), −1.1 (N)	111 (M), 91 (N)
Xie[b]	N	Obs TTE	1/2022–11/2022	US(VA)	70%	≥1 RF	Vaccination/immune status	HD	3.6 (vax)	2.4 (vax)	−1.2 (vax)	83 (vax)
Xie	M	Obs TTE	1/2022–9/2022	US(VA)	83%	≥1 RF	Vaccination status	HD	3.8	2.7	−1.1	91
Dryden-Peterson	N	Obs TTE	1/2022–7/2022	US	90%	>50		HD	1	0.6	−0.4	250
Aggarwal	N	Obs PS	3/2022–8/2022	US	79%	All eligible		H	1.4	0.9	−0.5	200
Faust	N	Obs PS	12/2021–7/2022	US	100%	All eligible	Cancer, CVD, pulm, no comorb	EHD	7	4.9	−2.1	47 (OR 0.93 if no comorb)
Dormuth	N	Obs PS	2/2022–2/2023	Canada	95%	3 high-risk	High IC, low IC, other risks	EHD	ND,3.4,3.7	ND,1.8,2.4	−2.5, −1.7, −1.3	40,60,75
Schwartz	N	Obs PS	4/2022–8/2022	Canada	100%	All eligible		HD	3.7	2.1	−1.6	62

M, molnupiravir; N, nirmatrelvir/ritonavir; R, remdesivir; VA, Department of Veterans Affairs; RF, risk factor; IC, immunocompromised; H, hospitalisation; D, death; E, emergency department visit; ND, no data; Vax, vaccinated; NNT, number needed to treat to prevent one outcome; NA, not applicable; OR, odds ratio. Only studies that were randomised trials (RCTs) or that used target trial emulation (TTE) or propensity score adjustment (PS) using observational (Obs) data are shown. [a]Risk differences in subsets: −2.9% first risk quartile (NNT 34), −0.7 s (NNT 143), 0.0 third/fourth; −1.9 immunocompromised (NNT 53). [b]Risk differences by immune status: −1.8% unvaccinated, −1.3% primary vaccination, −1.0% boosted; −1.4 first infection, −0.8% re-infection.

Table 3: **Summary of the literature on antiviral treatment of mild-to-moderate COVID-19.**

clinical practice. Although sex and prior infection with SARS-CoV-2 were not in the top 26 variables when not included *a priori*, we advise continuing to include them for the purpose of generalisability on the basis of data from multiple healthcare systems. There are relatively few women in the VA system, and since our study was designed to minimise the possibility of misclassifying resolved infections as active, the number of patients with a history of prior infection was far lower than will be seen with real-world use. A major strength of the prediction tool is that it accounts for fluctuations in absolute risk by using a short window of close to contemporaneous data, rather than an averaged risk that includes periods with different resources and risk. This advancement led to improvements in model performance when compared to other strategies for adjusting to longitudinal change, including stratification and direct adjustment for major circulating variant. In addition, we found improvements in model performance and calibration when additional variables were added and when the model included a 28-day rolling risk of severe disease estimate rather than longer window periods, highlighting the benefits of near-time data versus older data that does not reflect current trends. Although we are not able to anticipate changes in viral variant in advance of evolution, the prediction tool is designed such that risk estimates can be updated to provide more accurate estimates on an ongoing basis to guide clinical management.

The selected model is based on logistic regression. Although use of more advanced models was a consideration, the logistic regression model performed similarly to these more complex strategies, such as random forest and XGBoost (sTable 4) and is more explainable and easier to implement, both important considerations when developing tools designed to improve point-of-care clinical decision making. Prior work and our group's own experience has also found that when highly refined variables developed based on clinical judgement are available, there is little benefit to more complex modelling strategies in terms of predictive utility with substantial negative trade-offs in terms of feasibility of translation into practice.[37] As for how those predictor variables were used, we did not have the means to assess severity of comorbidities with confidence and anticipated that users would be in the same position. It was important to not model age as a linear continuous variable. We chose to use discrete categories to account for nonlinearity, but an alternative approach would be calculation of splines, which users in other healthcare systems could compare to the approach we used.

There are several limitations to our study. First, the data were developed using a cohort of vaccinated US Veterans. Compared to the general US population, Veterans are predominantly male, older, and white and Black individuals are over-represented while Asian and Hispanic individuals are under-represented. Thus, risk estimates based on data from the VA may not perform as well for other populations, particularly those involving children and higher proportions of female patients. However, we did estimate models stratified by sex, race, and ethnicity and found similar performance across different groups. Despite these caveats, risk factors for severe breakthrough infections were similar in the US Veteran population and other populations that include a different distribution of demographic groups, somewhat mitigating this concern.[14,18] Similarly, use of antivirals averaged about 23% in the VA from May, 2022, through January, 2023, and performance of the model might differ in systems with much lower current use.[38] However, the similar performance of the model in the Development era (when many infections occurred before antivirals were commonly used) and the Prospective Validation era is reassuring. Second, comorbidity phenotyping is purely based on CCW and ICD-10 codes and may be inaccurate, although the structured nature of these variables increases electronic health record implementation feasibility. This limitation does not apply to the medication exposure variables, which were based on actual administrations and dispenses. Third, classification of medication-exposures was based on clinical expertise rather than clearly defined categories; thus, others may have organised immune suppressive medications differently. Fourth, the list of medications used as risk predictors is long and includes both oral and intravenous medications. While this allowed us to include granular and time-varying information about risk of immune suppression from medications, it does introduce complexity and implementation challenges. Non-closed healthcare systems may not have medication administration data readily available, potentially complicating real-world use. Fifth, some miscalibration was observed at mid to high absolute predicted risk levels in the prospective validation. Specifically, the model tended to slightly under-estimate risk among higher-risk individuals (e.g., >10% risk of severe disease). However, a typical treatment threshold would be greater than 5% risk of severe outcome and the miscalibration occurred above these clinical treatment thresholds, such that if used to support outreach efforts these patients would still be captured. Precision at very high levels of risk is not essential, since most clinicians would agree that absolute risk >20% merits maximisation of booster vaccination, planning to provide antiviral treatment quickly in the event of infection, administration of monoclonal antibodies if available, and a low threshold for advising benign behavioural interventions to reduce risk of exposure. Sixth, our definition of severe COVID-19, as confronted by authors of numerous studies, involves arbitrary decisions, and attribution of hypoxemia or death to COVID-19 could not be achieved without chart review. We have previously reported that in the VA system, the percentage of deaths within 28 days of infection that were truly

COVID-19-related was 47% by mid-2022. However, death occurred in only 12% of patients classified as severe COVID-19 in this study, indicating that misclassification on the basis of death contributed little to the model. We feel that potential over-counting on the basis of death is preferable to over-counting on the basis of all-cause hospitalisation, as has been used in many studies, and conversely that under-counting by requiring documentation of hypoxemia would inappropriately minimise the effects of systemic illness among patients with advanced age or severe comorbidities. Seventh, the analysis of the effects of antivirals was limited by not being able to ascertain early use of remdesivir and by having to use calculations based on chart review in order to estimate risk differences and NNT. However, the goal of that analysis was not to make the most rigorous assessment of effect, as has already been done using target trial emulations, but to provide novel data across multiple strata of risk. The use of such strata, derived from a 25-variable model, should mitigate concerns about critical imbalances between treated and untreated patients. Eighth, the cohort for model development was limited to those with previous COVID-19 vaccination. This decision was made out of concern for missing data and unmeasurable confounders among the "unvaccinated" patients. Although limiting to vaccinated patients may have limited interpretability early in the pandemic, since the initial omicron wave that started in December 2021, the vast majority of the US population has developed immunity, via vaccination, natural infection, or both. It remains possible that the model does not generalise to those who acquired immunity via natural infection or to those without any exposure to the virus or the vaccine. However, the consistent finding that age, chronic kidney disease, chronic pulmonary disease, and immune suppression are important risk factors for severe disease across multiple studies and populations suggests that the risk prediction model will provide useful information for non-Veteran populations. Finally, we did not attempt to ascertain if multiple booster doses of vaccine were administered or to model multiple infections occurring after vaccination because of concerns about data reliability and missing data. More precise vaccine administration data might impact absolute risk of severe disease and therefore model predictive utility.

In conclusion, dynamic solutions are needed to provide patients with the most relevant and up-to-date information about their health. This COVID-19 risk prediction tool is designed to provide an adaptive measure of absolute risk to facilitate decision making about treatment and repeat vaccinations. Our next step is a pilot programme to embed the tool in the VA EHR at several sites and to develop an integrated application that can be used to support dissemination of evidence-based interventions to high-risk patients. The framework of the dynamic risk model is a proof-of-concept that near-real time data can be integrated and applied to support adaptive risk prediction at both the patient and population levels in other settings as part of a Learning Health System.

Contributors

All authors contributed significantly to the work. Conceptualisation: WBE, PM, NF Data curation (including data access): NF, AV, JL, KS Formal analysis (including data verification): NF, KS Funding acquisition: MB, ND, NF Investigation: KS, NF, PM, WBE Methodology: KS, NF, PM, WBE Project administration: KS, NF Resources: KS, NF, ND, MB Supervision: NF, PM, WBE Validation: KS, NF, JL Writing—original draft: KS, WBE, PM Writing—review & editing: KS, NF, AV, JL, DE, MB, ND, PM, WBE.

Data sharing statement

Patient level data cannot be shared due to privacy laws. Code underlying the data will be made available upon request to the authors.

Declaration of interests

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2025.103114.

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