

1 **Supplemental Data**

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3 **Table of Contents**

4

5	Supplemental Data 1	2
6	Supplemental Data 2	3
7	Supplemental Data 3	3
8	Supplemental Data 4	3
9	Table S1	4
10	Table S2	4
11	Table S3	6
12	Table S4	7
13	Table S5	8
14	Table S6	10
15	Table S7	10
16	Table S8	13
17	Table S9	14
18	Table S10	14
19	Table S11	15
20	Table S12	15
21	Table S13	15
22	Table S14	16
23	Table S15	16
24	Table S16	16
25	Table S17	19
26	Supplemental Figure Legends	20
27	Figure S1	21
28	Figure S2	22
29	Figure S3	23
30	Figure S4.....	24

31 **Supplemental Data 1: TRIPOD checklist for prediction model validation**

Section/Topic		Checklist Item	Page
Title and abstract			
Title	1	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract	2	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	2
Introduction			
Background and objectives	3a	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	3-4
	3b	Specify the objectives, including whether the study describes the development or validation of the model or both.	3-4
Methods			
Source of data	4a	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	5
	4b	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	5
Participants	5a	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	5
	5b	Describe eligibility criteria for participants.	5
	5c	Give details of treatments received, if relevant.	NA
Outcome	6a	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	5
	6b	Report any actions to blind assessment of the outcome to be predicted.	NA
Predictors	7a	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	5
	7b	Report any actions to blind assessment of predictors for the outcome and other predictors.	NA
Sample size	8	Explain how the study size was arrived at.	5
Missing data	9	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	5
Statistical analysis methods	10c	For validation, describe how the predictions were calculated.	6-7
	10d	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	6-7
	10e	Describe any model updating (e.g., recalibration) arising from the validation, if done.	6-7
Risk groups	11	Provide details on how risk groups were created, if done.	6
Development vs. validation	12	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	Table S7
Results			
Participants	13a	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	Fig S1
	13b	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	Table 1
	13c	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	Table S7
Model performance	16	Report performance measures (with CIs) for the prediction model.	8-9
Model-updating	17	If done, report the results from any model updating (i.e., model specification, model performance).	8-9
Discussion			
Limitations	18	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	12
Interpretation	19a	For validation, discuss the results with reference to performance in the development data, and any other validation data.	8-9
	19b	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	10-11

Implications	20	Discuss the potential clinical use of the model and implications for future research.	10-11
Other information			
Supplementary information	21	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	13
Funding	22	Give the source of funding and the role of the funders for the present study.	13

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Supplemental Data 2: Imputation of missing data using surrogate values and multivariate imputation by chained equations.

Encounters with respiratory or renal failure on admission were assigned highest scores for RR and SpO2 or urea, respectively. Encounters in which GCS was missing or there were no ICD-10 codes for acute encephalopathy, and billing codes for brain imaging or encephalography were present on hospital day 1, were assigned highest scores for neurologic function (Supplemental Table 2). Multiple imputation was carried out using the multivariate imputation by chained equations (MICE) via predictive mean matching (PMM) algorithm. Patterns of missingness for the four variables that had missing data – respiratory rate (RR), peripheral oxygen saturation on room air (SpO2), urea, and C-reactive protein (CRP) – are summarized in Supplemental Table 4. The set of predictors that were used to impute missing data for each variable is listed in Supplemental Table 5. A variable in this table has a value of 1 if it serves as a predictor to impute the target variable, and a value of 0 if it is not. The construction of this predictor matrix was guided by clinical and statistical judgment. Potential predictors with high level of missing values and/or low variance were excluded.

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Supplemental Data 3: Surge-index calculation.

COVID-19 cases were assigned weighting according to degree of illness severity as previously described [16], with higher weighting for higher degree of illness: i) COVID-19 patients requiring mechanical ventilation, ii) COVID-19 patients admitted to the intensive care unit (ICU) or requiring high-risk non-invasive ventilation (defined in Table S2); iii) COVID-19 patients that did not meet the above two criteria). i) COVID-19 patients requiring mechanical ventilation, ii) COVID-19 patients admitted to the intensive care unit (ICU) or requiring high-risk non-invasive ventilation (defined in Table S2); iii) COVID-19 patients that did not meet the above two criteria). The sum of weighted COVID-19 cases over each month for each hospital was divided by pre-pandemic bed capacity of the respective hospitals and multiplied by a factor of 10 to give the surge index value for that hospital-month.

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Supplemental Data 4: Handling multiple imputed datasets to generate AUC point estimates and confidence intervals.

First, 100 imputations of missing data were performed, each with 5 iterations, to generate 100 complete datasets for each pandemic wave. AUC, sensitivity, specificity, positive predictive value, and negative predictive value were calculated for 4C, m4C, and m4C without age within each imputed data set for Wave 1 and for m4C alone within each imputed data set for Wave 1, Wave 2, Wave 3, Delta, and early Omicron. Values from parallel imputed data sets were pooled by applying Rubin’s rule to generate point estimates. To assess the variation of those estimates, bootstrap based 95% confidence intervals were computed. We first sampled the data with replacement 1,000 times and for each of the resamples, 100 imputations were created. The point estimate for each bootstrap iteration was obtained by averaging the estimates across the 100

75 imputations. The procedure of bootstrap resampling followed by multiple imputation within each
 76 bootstrap iteration approximates the sampling distribution for each statistic of interest. The 95%
 77 bootstrap confidence interval for each estimate was computed using the 2.5th and the 97.5th
 78 percentiles of the bootstrap distribution.

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 81 **Table S1:** Diagnostic codes used to capture COVID-19 cases and comorbid and acute conditions
 82 for 4C and m4C score calculation.

Diagnosis	ICD-10 codes
COVID-19	March 2020 only: B97.29 + one of the following: J12.89, J12.81, J12.9, J18.0, J18.1, J18.2, J18.8, J18.9, J20.8, J20.9, J40, J22, J98.8, J98.9, J98.0, J98.01, J98.09, J98.1, J98.11, J98.19, J80, J96, J96.0, J96.00, J96.01, J96.02, J96.2, J96.20, J96.21, J96.22, J96.9, J96.90, J96.91, J96.92 March 2020 – January 2022: U07.1, J12.82
Chronic cardiac disease	I21.x, I22.x, I25.2, I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5-I42.9, I43.x, I50.x, P29.0
Chronic respiratory disease	I27.8, I27.9, J40.x-J44.x, J47.x, J60.x-J67.x, J68.4, J70.1, J70.3
Chronic renal disease (eGFR ≤30 ml/min)	I12.0, I13.1, N03.2-N03.7, N05.2-N05.7, N18.x, N19.x, N25.0, Z49.0-Z49.2, Z94.0, Z99.2
Mild to severe liver disease	B18.x, K70.0-K70.3, K70.9, K71.3-K71.5, K71.7, K73.x, K74.x, K76.0, K76.2-K76.4, K76.8, K76.9, Z94.4, I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7
Dementia	F00.x-F03.x, F05.1, G30.x, G31.1
Chronic neurological conditions	G45.x, G46.x, H34.0, I60.x-I69.x, G04.1, G11.4, G80.1, G80.2, G81.x, G82.x, G83.0-G83.4, G83.9
Connective tissue disease	M05.x, M06.x, M31.5, M32.x-M34.x, M35.1, M35.3, M36.0
Diabetes mellitus	E10.0, E10.1, E10.6, E10.8, E10.9, E11.0, E11.1, E11.6, E11.8, E11.9, E12.0, E12.1, E12.6, E12.8, E12.9, E13.0, E13.1, E13.6, E13.8, E13.9, E14.0, E14.1, E14.6, E14.8, E14.9, E10.2-E10.5, E10.7, E11.2-E11.5, E11.7, E12.2-E12.5, E12.7, E13.2-E13.5, E13.7, E14.2-E14.5, E14.7
HIV/ AIDS	B20.x-B22.x, B24.x
Malignancy	C00.x-C26.x, C30.x-C34.x, C37.x-C41.x, C43.x, C45.x-C58.x, C60.x-C76.x, C81.x-C85.x, C88.x, C90.x-C97.x, C77.x-C80.x
Obesity	E66.0, E66.1, E66.2, E66.8, E66.9, Z68.3, Z68.4
Encephalopathy	R40.1, R40.2, R40.3, R40.4, G92.x, G93.4, E51.2, I67.4, I67.83, K72.91
Chronic renal disease stage 5 or end-stage renal disease	Z99.2, I13.11, I12.0, N18.5, N18.6

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 84 **Table S2:** m4C score rubric.

Category	Variable	Points

Age*	Age (years)	
	<50	0
	50-59	2
	60-69	4
	70-79	6
	≥80	7
Gender*	Gender	
	Female	0
	Male	1
Comorbid disease [†]	Number of comorbidities	
	0	0
	1	1
	≥2	2
Respiratory rate	Respiratory rate (breaths/min) [‡]	
	<20	0
	20-29	1
	≥30	2
	Need for MV or high-risk NIV [§] on hospital day 1	2
Oxygen saturation	Peripheral oxygen saturation on room air (%) [‡]	
	≥92	0
	<92	2
	Oxygen saturation calculated from partial pressure of oxygen on arterial blood gas	
	≥92	0
	<92	2
	Need for MV or high-risk NIV [§] on hospital day 1	2
Neurologic function	Glasgow coma scale score [‡]	
	15	0
	<15	2
	Billing code for electroencephalography or brain imaging on hospital day 1	2
	ICD-10 code for encephalopathy present-on-admission [†]	2
Urea	Urea (mmol/L)	
	<7	0
	7-14	1
	>14	3
	Procedure code for renal replacement therapy on hospital day 1**	3

	ICD-10 code for chronic renal disease stage 5 or end-stage renal disease present-on-admission [†]	3
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MV = mechanical ventilation; NIV = non-invasive ventilation.
 *Age and sex were available from encounter administrative data.
[†]Co-morbidities, acute encephalopathy, and chronic renal disease were identified using ICD-10 codes present-on-admission for the index encounter or within any prior encounter within PINC-AI in the preceding 1 year (Table S1).
[‡]First recorded value of vital signs were obtained from encounter day 1.
[§]High-risk NIV refers to NIV other than for pre-existing obstructive sleep apnea or obesity hypoventilation syndrome [16].
^{||}First recorded value of laboratory values were obtained from encounter days 1-2.
 Oxygen saturation calculated from partial pressure of arterial oxygen, using Severinghaus equation.
 **Renal replacement therapy captured using ICD-PCS codes 5A1D70Z, 5A1D80Z, 5A1D90Z or 3E1M39Z.

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Table S3: 4C and m4C without age score rubrics.

Category	Variable	4C score points	m4C without age score points
Age*	Age (years)		
	<50	0	0
	50-59	2	0
	60-69	4	0
	70-79	6	0
	≥80	7	0
Gender*	Gender		
	Female	0	0
	Male	1	1
Comorbid disease [†]	Number of comorbidities		
	0	0	0
	1	1	1
	≥2	2	2
Respiratory rate	Respiratory rate (breaths/min) [‡]		
	<20	0	0
	20-29	1	1
	≥30	2	2
	Need for MV or high-risk NIV [§] on hospital day 1	2	2
Oxygen saturation	Peripheral oxygen saturation on room air (%) [‡]		
	≥92	0	0
	<92	2	2

	Oxygen saturation calculated from partial pressure of oxygen on arterial blood gas ^{ll}		
	≥92	0	0
	<92	2	2
	Need for MV or high-risk NIV [§] on hospital day 1	2	2
Neurologic function	Glasgow coma scale score [‡]		
	15	0	0
	<15	2	2
	Billing code for electroencephalography or brain imaging on hospital day 1	2	2
	ICD-10 code for encephalopathy [†] present-on-admission	2	2
Renal function	Urea (mmol/L) ^{ll}		
	<7	0	0
	7-14	1	1
	>14	3	3
	Procedure code for renal replacement therapy on hospital day 1 ^{**}	3	3
	ICD-10 code for chronic renal disease stage 5 or end-stage renal disease [†] present-on-admission	4	4
C-reactive protein	C-reactive protein (mg/L) ^{ll}		
	<50	0	NA
	50-99	1	NA
	≥100	2	NA

MV = mechanical ventilation; NIV = non-invasive ventilation.

*Age and sex were available from encounter administrative data.

†Co-morbidities, acute encephalopathy, and chronic renal disease were identified using ICD-10 codes present-on-admission for the index encounter or within any prior encounter within PINC-AI in the preceding 1 year (Table S1).

‡First recorded value of vital signs were obtained from encounter day 1.

§High-risk NIV refers to NIV other than for pre-existing obstructive sleep apnea or obesity hypoventilation syndrome [16].

^{ll}First recorded value of laboratory values were obtained from encounter days 1-2.

Oxygen saturation calculated from partial pressure of arterial oxygen, using Severinghaus equation.

**Renal replacement therapy captured using ICD-PCS codes 5A1D70Z, 5A1D80Z, 5A1D90Z or 3E1M39Z.

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Table S4: Missingness of individual m4C and 4C score components.

Score Component	Missing, N (%)
Age	0 (0%)
Gender	0 (0%)

No. comorbidities*	0 (0%)
Respiratory rate	148,165 (49.7%)
Oxygen saturation	156,194 (52.4%)
Acute encephalopathy*	0 (0%)
Glasgow coma scale score	282,965 (94.8%)
Urea	84,747 (28.4%)
C-reactive protein [†]	153,197 (51.3%)

91 *Missing values (i.e., absent coding) imputed as normal.

92 [†]For 4C score only.

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Table S5: Predictor matrix of multiple imputation models.

Variable names	To impute respiratory rate [RR]	To impute peripheral oxygen saturation on room air [SpO2]	To impute urea	To impute C-reactive protein [CRP]*
Admission wave [†]	1	1	1	1
Binary indicator for encounters with COVID as primary encounter diagnosis; 2 for encounters with COVID as secondary encounter diagnosis	1	1	1	1
Age in years	1	1	1	1
Gender	1	1	1	1
4C score for GCS	1	1	1	1
Mapped race/ethnicity	1	1	1	1
Mapped admission source	1	1	1	1
Hospital beds count	1	1	1	1
Hospital teaching status	1	1	1	1
Hospital urban/ rural status	1	1	1	1
Census region of hospital	1	1	1	1
Binary indicator for encounters with either ICD10 codes POA or present in prior encounter history for Chronic cardiac disease	1	1	1	1
Binary indicator for encounters with either ICD10 codes POA or present in prior encounter history for Chronic respiratory disease (excluding asthma)	1	1	1	1

Binary indicator for encounters with either ICD10 codes POA or present in prior encounter history for Chronic renal disease (eGFR <=30)	1	1	1	1
Binary indicator for encounters with either ICD10 codes POA or present in prior encounter history for Mild to severe liver disease	1	1	1	1
Binary indicator for encounters with either ICD10 codes POA or present in prior encounter history for Dementia	1	1	1	1
Binary indicator for encounters with either ICD10 codes POA or present in prior encounter history for Chronic neurological conditions	1	1	1	1
Binary indicator for encounters with either ICD10 codes POA or present in prior encounter history for Connective tissue disease	1	1	1	1
Binary indicator for encounters with either ICD10 codes POA or present in prior encounter history for Diabetes mellitus	1	1	1	1
Binary indicator for encounters with either ICD10 codes POA or present in prior encounter history for HIV/ AIDS	1	1	1	1
Binary indicator for encounters with either ICD10 codes POA or present in prior encounter history for Malignancy	1	1	1	1
Binary indicator for encounters with either ICD10 codes POA or present in prior encounter history for Obesity	1	1	1	1
Binary indicator for encounters with MV based on ICD-PCS codes on Day 1	0	0	1	1

Binary indicator for encounters with High-risk NIV based on ICD-PCS code on Day 1	0	0	1	1
Binary indicator for encounters with Encephalopathy ICD-10 coding (diagnosis POA)	1	1	1	1
Binary indicator for encounters with billing codes for CT head/ MR head/ EEG on Day 1-2	1	1	1	1
Binary indicator for encounters with ICD10 codes POA for Chronic RRT	1	1	0	1
Binary indicator for encounters with ICD-PCS codes for Acute RRT on Day 1	1	1	0	1
Binary indicator for encounters with positive lab diagnosis of COVID	1	1	1	1

96 GCS = Glasgow Coma Scale score; POA = Present-on-admission; eGFR = Estimated glomerular
 97 filtration rate; NIV = Non-invasive ventilation; MV = Mechanical ventilation; CT = Computerized
 98 tomography; MR = Magnetic resonance imaging; RRT = Renal replacement therapy.

99 *For 4C only, as CRP is not a component of m4C.

100 †Included as an imputation predictor in the analysis that involves all the five pandemic waves. For wave-
 101 specific analyses, it was excluded.

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104 **Table S6:** Sensitivity, specificity, positive predictive value, and negative predictive value of
 105 m4C score during Wave 1 using different score cutoffs.

m4C Score Cutoff	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
≥6	91.7%	44.0%	22.0%	96.8%
≥7	87.5%	52.3%	24.1%	96.0%
≥8	80.9%	60.4%	26.1%	94.8%
≥9	72.9%	68.8%	28.8%	93.6%

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108 **Table S7:** Characteristics of adult COVID-19 hospitalizations in 281 hospitals in PINC-AI (1
 109 March 2020 – 31 January 2022).

Characteristic	Overall, N = 298,379	Wave 1, N = 14,542	Wave 2, N = 37,175	Wave 3, N = 128,780	Delta, N = 91,250	Early Omicron, N = 26,632
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Demographics						
Age in years, median (IQR)	62 (48, 73)	61 (48, 72)	61 (47, 73)	64 (51, 75)	59 (45, 71)	63 (47, 75)
Sex						
Female	146,201 (49%)	6,820 (47%)	18,622 (50%)	62,359 (48%)	44,615 (49%)	13,785 (52%)
Male	152,178 (51%)	7,722 (53%)	18,553 (50%)	66,421 (52%)	46,635 (51%)	12,847 (48%)
Race						
Hispanic	43,646 (15%)	3,305 (23%)	8,971 (24%)	18,080 (14%)	10,128 (11%)	3,162 (12%)
Non-Hispanic Black	55,015 (18%)	3,760 (26%)	8,864 (24%)	22,425 (17%)	14,965 (16%)	5,001 (19%)
Non-Hispanic White	174,433 (58%)	5,605 (39%)	16,041 (43%)	76,929 (60%)	59,431 (65%)	16,427 (62%)
Other	25,285 (8.5%)	1,872 (13%)	3,299 (8.9%)	11,346 (8.8%)	6,726 (7.4%)	2,042 (7.7%)
Admission source						
Home	257,492 (86%)	12,060 (83%)	32,044 (86%)	110,845 (86%)	79,823 (87%)	22,720 (85%)
Acute Care Facility	21,858 (7.3%)	871 (6.0%)	2,866 (7.7%)	10,271 (8.0%)	6,269 (6.9%)	1,581 (5.9%)
Subacute Facility	9,301 (3.1%)	1,224 (8.4%)	1,247 (3.4%)	4,003 (3.1%)	1,947 (2.1%)	880 (3.3%)
Other	9,728 (3.3%)	387 (2.7%)	1,018 (2.7%)	3,661 (2.8%)	3,211 (3.5%)	1,451 (5.4%)
Hospital features						
Bed count						
0-99	26,904 (9.0%)	562 (3.9%)	2,298 (6.2%)	11,318 (8.8%)	10,221 (11%)	2,505 (9.4%)
100-199	50,394 (17%)	2,139 (15%)	6,130 (16%)	21,812 (17%)	16,520 (18%)	3,793 (14%)
200-299	49,645 (17%)	2,090 (14%)	5,600 (15%)	22,381 (17%)	15,095 (17%)	4,479 (17%)
300-399	54,147 (18%)	3,033 (21%)	6,362 (17%)	24,045 (19%)	15,828 (17%)	4,879 (18%)
400-499	21,742 (7.3%)	892 (6.1%)	2,790 (7.5%)	9,334 (7.2%)	7,019 (7.7%)	1,707 (6.4%)
500+	95,547 (32%)	5,826 (40%)	13,995 (38%)	39,890 (31%)	26,567 (29%)	9,269 (35%)
Teaching status	119,731 (40%)	8,118 (56%)	14,173 (38%)	52,649 (41%)	33,362 (37%)	11,429 (43%)
Location						
Rural	50,731 (17%)	1,299 (8.9%)	6,126 (16%)	21,284 (17%)	17,705 (19%)	4,317 (16%)
Urban	247,648 (83%)	13,243 (91%)	31,049 (84%)	107,496 (83%)	73,545 (81%)	22,315 (84%)
Census region						

Midwest	57,622 (19%)	3,749 (26%)	4,969 (13%)	25,324 (20%)	19,148 (21%)	4,432 (17%)
Northeast	35,060 (12%)	3,810 (26%)	1,699 (4.6%)	17,155 (13%)	8,314 (9.1%)	4,082 (15%)
South	195,542 (66%)	6,952 (48%)	29,523 (79%)	83,053 (64%)	59,551 (65%)	16,463 (62%)
West	10,155 (3.4%)	31 (0.2%)	984 (2.6%)	3,248 (2.5%)	4,237 (4.6%)	1,655 (6.2%)
Comorbidities						
Chronic cardiac disease	64,556 (22%)	3,024 (21%)	7,279 (20%)	29,073 (23%)	17,711 (19%)	7,469 (28%)
Chronic respiratory disease	51,363 (17%)	2,207 (15%)	5,549 (15%)	22,888 (18%)	14,753 (16%)	5,966 (22%)
Chronic renal disease	64,111 (21%)	3,317 (23%)	7,817 (21%)	29,469 (23%)	16,617 (18%)	6,891 (26%)
Chronic liver disease	21,213 (7.1%)	888 (6.1%)	2,242 (6.0%)	9,038 (7.0%)	6,729 (7.4%)	2,316 (8.7%)
Dementia	23,293 (7.8%)	1,887 (13%)	3,578 (9.6%)	10,242 (8.0%)	5,086 (5.6%)	2,500 (9.4%)
Chronic neurologic disease	22,347 (7.5%)	1,070 (7.4%)	2,428 (6.5%)	9,833 (7.6%)	6,105 (6.7%)	2,911 (11%)
Connective tissue disease	10,762 (3.6%)	448 (3.1%)	1,167 (3.1%)	4,944 (3.8%)	3,056 (3.3%)	1,147 (4.3%)
Diabetes mellitus	91,029 (31%)	4,873 (34%)	11,933 (32%)	41,658 (32%)	23,803 (26%)	8,762 (33%)
HIV/ AIDS	1,029 (0.3%)	78 (0.5%)	149 (0.4%)	427 (0.3%)	264 (0.3%)	111 (0.4%)
Malignancy	18,774 (6.3%)	750 (5.2%)	1,865 (5.0%)	8,525 (6.6%)	5,349 (5.9%)	2,285 (8.6%)
Obesity	68,639 (23%)	2,774 (19%)	8,159 (22%)	29,672 (23%)	22,270 (24%)	5,764 (22%)
m4C Score Components						
No. of comorbidities	1 (0, 2)	1 (0, 2)	1 (0, 2)	1 (0, 2)	1 (0, 2)	1 (0, 3)
Oxygen saturation by co-oximetry (%) , median (IQR)	95 (92, 98)	96 (93, 98)	96 (93, 98)	95 (93, 97)	95 (92, 97)	96 (93, 98)
Oxygen saturation from blood gas (%) , median (IQR)	93 (88, 96)	94 (89, 97)	93 (88, 96)	93 (88, 97)	92 (86, 96)	93 (86, 97)
Respiratory rate (breaths per minute), median (IQR)	20 (18, 22)	20 (18, 24)	20 (18, 22)	20 (18, 22)	20 (18, 23)	18 (18, 22)
Neurologic function						
Normal	262,372 (88%)	12,899 (89%)	32,877 (88%)	113,283 (88%)	81,288 (89%)	22,025 (83%)
Abnormal	36,007 (12%)	1,643 (11%)	4,298 (12%)	15,497 (12%)	9,962 (11%)	4,607 (17%)
Urea (mmol/L), median (IQR)	6.1 (4.3, 9.6)	5.7 (3.9, 9.6)	5.7 (3.9, 9.3)	6.4 (4.3, 10.0)	6.1 (4.3, 9.3)	6.8 (4.3, 11.1)
Mechanical ventilation	9,770 (3.3%)	874 (6.0%)	1,267 (3.4%)	3,894 (3.0%)	2,929 (3.2%)	806 (3.0%)

Non-invasive ventilation	4,521 (1.5%)	107 (0.7%)	310 (0.8%)	1,805 (1.4%)	1,974 (2.2%)	325 (1.2%)
Renal replacement therapy	2,927 (1.0%)	208 (1.4%)	379 (1.0%)	1,214 (0.9%)	709 (0.8%)	417 (1.6%)
Outcome						
Survival	262,679 (88%)	12,401 (85%)	33,068 (89%)	113,946 (88%)	79,387 (87%)	23,877 (90%)
Death	29,239 (9.8%)	1,672 (11%)	3,251 (8.7%)	12,042 (9.4%)	10,191 (11%)	2,083 (7.8%)
Hospice	6,461 (2.2%)	469 (3.2%)	856 (2.3%)	2,792 (2.2%)	1,672 (1.8%)	672 (2.5%)

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Table S8: Main features of study cohort and the 4C and m4C development cohorts.

Feature	Study cohort	4C development cohort*	m4C development cohort[†]
Data source	Administrative database	COVID-19 registry drawing from case report forms	COVID-19 registry drawing from case report forms and electronic healthcare records, supplemented by chart review
Facilities	281 U.S. hospitals	260 U.K. hospitals	40 U.S. medical centers
Patients	Adult hospital inpatients and adult patients who died in the emergency room or under observation status, with primary or secondary ICD-10 coding for COVID-19 or laboratory test positivity for SARS-CoV-2. Excluding individuals with DNR status and those with unknown sex.	Adult hospital inpatients with “high likelihood of infection with SARS-CoV-2.	Adult patients testing positive for SARS-CoV-2 and hospitalized from the emergency room. Excluding individuals with DNR status.
Study period	March 2020 – January 2022	February – May 2020	March 2020 – September 2020
Outcome	In-hospital mortality or discharge to hospice	In-hospital mortality	Mortality at 30 days
Crude mortality	12.0%	32.2%	16.9%
Age (years)			
<50	27.1%	13.8%	20.8%
50-69	40.1%	28.9%	43.5%
70-79	19.4%	22.7%	19.1%
≥80	13.4%	34.6%	16.5%
Sex distribution	49% female	41.7% female	44% female

No. comorbidities			
0	32.5%	24.0%	38.7%
1	27.5%	28.0%	32.5%
≥2	40.0%	48.0%	28.9%
Oxygen saturation (%)	93 (88-96)	94.0 (6.0)	Aggregate not reported
Respiratory rate (breaths/min)	20 (18-22)	22.0 (9.0)	20 (18-23)
Glasgow coma scale score	15.0 (0.0)	15.0 (0.0)	NA
Acute encephalopathy	12%	NA	14.1%
Urea	6.1 mmol/L (4.3-9.6)	7.0 mmol/L (6.3)	18 mg/dL (12-31)
C-reactive protein (mg/L)	79 (35-140)	84.9 (122.0)	Aggregate not reported

113 *Knight SR, *et al.* BMJ 2020

114 †Gordon AJ, *et al.* BMJ Open 2022

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Table S9: Crude mortality of COVID-19 patients by m4C in the overall cohort and by pandemic wave.

m4C score	Overall*	Wave 1*	Wave 2*	Wave 3*	Delta*	Early Omicron*
0-2	1.3	1.2	0.8	1.1	2.1	0.8
3-4	3.9	3.5	3.1	2.8	5.6	3.2
5-6	7.5	6.6	6.1	5.7	11	5.8
7-8	11.3	13.5	10.6	9.9	14.4	8.4
9-10	15.8	20	16	14.6	18	12.6
11-12	22.6	30.8	24.9	21.9	23.4	17.1
13-14	32.7	42.2	36.4	32.1	33.7	24.6
15-16	48.7	63.6	55.3	47.4	46.5	44.3
≥17	65.6	81.5	64.9	63.4	63.4	72.2

119 *COVID-19 deaths (% of all COVID-19 encounters) for each m4C score result in the overall cohort and
120 by pandemic wave.

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Table S10: Distribution of hospital-month surge index by pandemic wave.

Surge category*	Surge index range	Wave 1	Wave 2	Wave 3	Delta	Early Omicron
		N = 528 [†]	N = 870 [†]	N = 2,148 [†]	N = 1,394 [†]	N = 215 [†]
Low (<50%)	<3.18	416 (78.8)	560 (64.4)	1,035 (48.2)	545 (39.1)	22 (10.2)
Moderate (≥50% to <75%)	≥3.18 - <6.93	70 (13.3)	217 (24.9)	600 (27.9)	380 (27.3)	23 (10.7)
High (≥75%)	≥6.93	42 (7.95)	93 (10.7)	513 (23.9)	469 (33.6)	170 (79.1)

*Surge category defined by distribution of surge index for every hospital-month in which there was a COVID-19 admission, stratified by percentile (surge index <50th, ≥50th to <75th, and ≥75th percentiles).
†Number of hospital months (%) within each surge category for each wave.

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Table S11: Crude mortality of COVID-19 patients by hospital-month surge category in the overall cohort and by pandemic wave.

Surge category	Overall*	Wave 1*	Wave 2*	Wave 3*	Delta*	Early Omicron*
Low (<50%)	9.07%	13.1%	9.44%	8.10%	8.56%	12.5%
Moderate (≥50% to <75%)	11.3%	15.4%	11.1%	10.4%	12.2%	8.86%
High (≥75%)	13.1%	15.8%	12.5%	13.2%	14.1%	10.4%

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*Number of COVID-19 deaths (% of all COVID-19 encounters) within each surge category in the overall cohort and by pandemic wave.

Table S12: Performance characteristics of m4C, 4C, and m4C without age in Wave 1.

Characteristic*	m4C Score Mean (95% CI)	4C Score Mean (95% CI)	m4C Score without age Mean (95% CI)
AUC	0.779 (0.769 – 0.789)	0.783 (0.773 – 0.793)	0.734 (0.723 – 0.744)
Sensitivity	0.917 (0.906 – 0.927)	0.824 (0.809 – 0.838)	0.663 (0.645 – 0.681)
Specificity	0.440 (0.431 – 0.448)	0.596 (0.588 – 0.604)	0.684 (0.676 – 0.692)
PPV	0.220 (0.212 – 0.229)	0.260 (0.251 – 0.271)	0.266 (0.255 – 0.277)
NPV	0.968 (0.964 – 0.972)	0.951 (0.947 – 0.956)	0.921 (0.916 – 0.926)

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AUC = area under receiver operating characteristic curve, PPV = positive predictive value, NPV = negative predictive value.

*Measures generated using score cutoffs of ≥9 and ≥6 for 4C and m4C scores, respectively.

Table S13: Performance characteristics of m4C by pandemic wave.

Cohort	AUC		Sensitivity		Specificity		PPV		NPV	
	Mean	95%CI	Mean	95%CI	Mean	95%CI	Mean	95%CI	Mean	95%CI
Wave 1	0.779	0.769-0.789	0.917	0.906-0.927	0.440	0.431-0.448	0.220	0.212-0.229	0.968	0.964-0.972
Wave 2	0.772	0.765-0.779	0.907	0.898-0.915	0.448	0.442-0.453	0.169	0.164-0.174	0.975	0.972-0.977
Wave 3	0.746	0.743-0.750	0.920	0.916-0.925	0.374	0.371-0.376	0.161	0.158-0.163	0.973	0.972-0.974
Delta	0.707	0.702-0.712	0.836	0.830-0.843	0.448	0.445-0.451	0.185	0.181-0.188	0.948	0.946-0.950
Early Omicron	0.729	0.721-0.738	0.923	0.913-0.932	0.355	0.349-0.361	0.142	0.137-0.147	0.975	0.972-0.978

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AUC = area under receiver operating characteristic curve, PPV = positive predictive value, NPV = negative predictive value.

142 **Table S14:** Inter-wave differences in AUCs of m4C score.

Comparison	Difference in AUCs Mean (95% CI*)	P-value*
Wave1 - Wave2	0.0042 (-0.0080 – 0.0165)	0.4981
Wave1 - Wave3	0.0309 (0.0200 – 0.0418)	<0.0001
Wave1 - Delta	0.0701 (0.0590 – 0.0813)	<0.0001
Wave1 - Omicron	0.0452 (0.0315 – 0.0589)	<0.0001
Wave2 - Wave3	0.0267 (0.0186 – 0.0348)	<0.0001
Wave2 - Delta	0.0659 (0.0574 – 0.0744)	<0.0001
Wave2 - Omicron	0.0410 (0.0293 – 0.0527)	<0.0001
Wave3 - Delta	0.0393 (0.0330 – 0.0455)	<0.0001
Wave3 - Omicron	0.0143 (0.0042 – 0.0244)	0.0056
Delta - Omicron	-0.0249 (-0.0354 – -0.0145)	<0.0001

*P-value and 95% confidence intervals from Delong’s test.

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Table S15: Inter-wave differences in sensitivity, specificity, and positive and negative predictive values of m4C score.

	Sensitivity		Specificity		PPV		NPV	
	Mean Diff*	95%CI†	Mean Diff*	95%CI†	Mean Diff*	95%CI†	Mean Diff*	95%CI†
Wave1 - Wave2	0.0130	-0.044 ~-0.0232	-0.0122	-0.0216 ~-0.0029	0.0497	0.0389 ~-0.0602	-0.0066	-0.0117 ~-0.0021
Wave1 - Wave3	-0.0033	-0.0157 ~-0.0083	0.0622	0.0539 ~-0.0707	0.0587	0.0493 ~-0.0672	-0.0048	-0.0095 ~-0.0005
Wave1 - Delta	0.0814	0.0685 ~-0.0933	-0.0131	-0.0217 ~-0.0049	0.0344	0.0256 ~-0.0436	0.0200	0.0150 ~-0.0245
Wave1 - Omicron	-0.0038	-0.0179 ~-0.0102	0.0769	0.0673 ~-0.0874	0.0771	0.0672 ~-0.0866	-0.0070	-0.0124 ~-0.0020
Wave2 - Wave3	-0.0137	-0.0227 ~-0.0035	0.0745	0.0687 ~-0.0805	0.0089	0.0037 ~-0.0146	0.0018	-0.0010 ~-0.0048
Wave2 - Delta	0.0711	0.0608 ~-0.0815	-0.0008	-0.0071 ~-0.0052	-0.0153	-0.0212 ~-0.0093	0.0266	0.0235 ~-0.0299
Wave2 - Omicron	-0.0142	-0.0263 ~-0.0005	0.0891	0.0812 ~-0.0961	0.0273	0.0206 ~-0.0342	-0.0004	-0.0043 ~-0.0036
Wave3 - Delta	0.0847	0.0770 ~-0.0921	-0.0753	-0.0798 ~-0.0712	-0.0242	-0.0283 ~-0.0205	0.0248	0.0222 ~-0.0272
Wave3 - Omicron	-0.0005	-0.0107 ~-0.0103	0.0146	0.0081 ~-0.0207	0.0184	0.0129 ~-0.0238	-0.0022	-0.0056 ~-0.0012
Delta - Omicron	-0.0853	-0.0967 ~-0.0736	0.0899	0.0825 ~-0.0964	0.0426	0.0369 ~-0.0486	-0.0270	-0.0309 ~-0.0232

*Mean difference across 100 imputed datasets.

†Bootstrap based 95% CIs (percentiles) around the mean difference.

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Table S16: Characteristics of adult COVID-19 hospitalizations in 182 hospitals in PINC-AI (1 March 2020 – 31 January 2022) – complete case records only.

Characteristic	Overall, N = 125,562	Wave 1, N = 6,635	Wave 2, N = 17,834	Wave 3, N = 58,303	Delta, N = 34,177	Early Omicron, N = 8,613
Age in years, median (IQR)	63 (50, 74)	61 (49, 72)	62 (50, 73)	64 (52, 75)	60 (47, 71)	65 (52, 75)
Sex						
Female	58,230 (46%)	2,921 (44%)	8,280 (46%)	26,934 (46%)	16,080 (47%)	4,015 (47%)
Male	67,332 (54%)	3,714 (56%)	9,554 (54%)	31,369 (54%)	18,097 (53%)	4,598 (53%)
Race						
Hispanic	21,915 (17%)	1,746 (26%)	4,999 (28%)	9,890 (17%)	4,321 (13%)	959 (11%)
Non-Hispanic Black	19,683 (16%)	1,349 (20%)	3,656 (21%)	8,249 (14%)	4,966 (15%)	1,463 (17%)
Non-Hispanic White	74,202 (59%)	2,614 (39%)	7,834 (44%)	35,323 (61%)	22,769 (67%)	5,662 (66%)
Other	9,762 (7.8%)	926 (14%)	1,345 (7.5%)	4,841 (8.3%)	2,121 (6.2%)	529 (6.1%)
Admission source						
Home	108,347 (86%)	5,412 (82%)	15,455 (87%)	50,345 (86%)	29,712 (87%)	7,423 (86%)
Acute Care Facility	10,394 (8.3%)	492 (7.4%)	1,442 (8.1%)	4,981 (8.5%)	2,823 (8.3%)	656 (7.6%)
Subacute Facility	4,033 (3.2%)	596 (9.0%)	628 (3.5%)	1,788 (3.1%)	757 (2.2%)	264 (3.1%)
Other	2,788 (2.2%)	135 (2.0%)	309 (1.7%)	1,189 (2.0%)	885 (2.6%)	270 (3.1%)
Bed count						
0-99	6,682 (5.3%)	122 (1.8%)	701 (3.9%)	2,791 (4.8%)	2,494 (7.3%)	574 (6.7%)
100-199	24,226 (19%)	1,127 (17%)	3,418 (19%)	11,384 (20%)	6,867 (20%)	1,430 (17%)
200-299	20,709 (16%)	1,047 (16%)	2,571 (14%)	10,694 (18%)	4,976 (15%)	1,421 (16%)
300-399	23,480 (19%)	1,561 (24%)	2,840 (16%)	11,198 (19%)	6,290 (18%)	1,591 (18%)
400-499	12,662 (10%)	500 (7.5%)	1,748 (9.8%)	5,376 (9.2%)	3,993 (12%)	1,045 (12%)
500+	37,803 (30%)	2,278 (34%)	6,556 (37%)	16,860 (29%)	9,557 (28%)	2,552 (30%)

Characteristic	Overall, N = 125,562	Wave 1, N = 6,635	Wave 2, N = 17,834	Wave 3, N = 58,303	Delta, N = 34,177	Early Omicron, N = 8,613
Teaching status	49,464 (39%)	3,450 (52%)	6,543 (37%)	24,100 (41%)	11,903 (35%)	3,468 (40%)
Urban location						
Rural	22,187 (18%)	573 (8.6%)	3,163 (18%)	9,715 (17%)	7,047 (21%)	1,689 (20%)
Urban	103,375 (82%)	6,062 (91%)	14,671 (82%)	48,588 (83%)	27,130 (79%)	6,924 (80%)
Census region						
Midwest	26,255 (21%)	1,988 (30%)	2,275 (13%)	11,932 (20%)	7,886 (23%)	2,174 (25%)
Northeast	13,605 (11%)	1,642 (25%)	778 (4.4%)	8,690 (15%)	1,676 (4.9%)	819 (9.5%)
South	84,376 (67%)	3,002 (45%)	14,746 (83%)	37,472 (64%)	23,823 (70%)	5,333 (62%)
West	1,326 (1.1%)	3 (<0.1%)	35 (0.2%)	209 (0.4%)	792 (2.3%)	287 (3.3%)
Chronic cardiac disease	28,246 (22%)	1,413 (21%)	3,689 (21%)	13,564 (23%)	6,933 (20%)	2,647 (31%)
Chronic respiratory disease	22,520 (18%)	995 (15%)	2,795 (16%)	10,718 (18%)	5,875 (17%)	2,137 (25%)
Chronic renal disease	27,099 (22%)	1,489 (22%)	3,758 (21%)	13,154 (23%)	6,296 (18%)	2,402 (28%)
Mild to severe liver disease	8,850 (7.0%)	392 (5.9%)	1,132 (6.3%)	4,034 (6.9%)	2,484 (7.3%)	808 (9.4%)
Dementia	10,193 (8.1%)	842 (13%)	1,944 (11%)	4,571 (7.8%)	1,963 (5.7%)	873 (10%)
Chronic neurologic conditions	9,259 (7.4%)	482 (7.3%)	1,236 (6.9%)	4,311 (7.4%)	2,234 (6.5%)	996 (12%)
Connective tissue disease	4,574 (3.6%)	205 (3.1%)	548 (3.1%)	2,267 (3.9%)	1,148 (3.4%)	406 (4.7%)
Diabetes mellitus	38,986 (31%)	2,156 (32%)	5,841 (33%)	19,017 (33%)	8,944 (26%)	3,028 (35%)
HIV/ AIDS	426 (0.3%)	35 (0.5%)	80 (0.4%)	178 (0.3%)	104 (0.3%)	29 (0.3%)
Malignancy	7,755 (6.2%)	325 (4.9%)	914 (5.1%)	3,818 (6.5%)	1,931 (5.6%)	767 (8.9%)
Obesity	30,439 (24%)	1,148 (17%)	4,267 (24%)	14,165 (24%)	8,826 (26%)	2,033 (24%)

Characteristic	Overall, N = 125,562	Wave 1, N = 6,635	Wave 2, N = 17,834	Wave 3, N = 58,303	Delta, N = 34,177	Early Omicron, N = 8,613
No. of comorbidities	1.00 (0.00, 2.00)	1.00 (0.00, 2.00)	1.00 (0.00, 2.00)	1.00 (0.00, 2.00)	1.00 (0.00, 2.00)	2.00 (1.00, 3.00)
Oxygen saturation by co-oximetry (%), median (IQR)	95.0 (92.0, 97.0)	95.0 (93.0, 98.0)	96.0 (93.0, 98.0)	95.0 (92.0, 97.0)	94.0 (91.0, 97.0)	96.0 (93.0, 98.0)
Oxygen saturation from blood gas (%), median (IQR)	93 (89, 97)	94 (90, 97)	93 (89, 97)	93 (89, 97)	93 (88, 96)	94 (88, 97)
Respiratory rate (breaths per minute), median (IQR)	20.0 (18.0, 23.0)	20.0 (18.0, 24.0)	20.0 (18.0, 22.0)	20.0 (18.0, 22.0)	20.0 (18.0, 24.0)	19.0 (18.0, 22.0)
Neurologic function						
Normal	108,795 (87%)	5,821 (88%)	15,375 (86%)	50,753 (87%)	29,971 (88%)	6,875 (80%)
Abnormal	16,767 (13%)	814 (12%)	2,459 (14%)	7,550 (13%)	4,206 (12%)	1,738 (20%)
Urea (mmol/L), median (IQR)	6.4 (4.3, 10.0)	5.7 (3.9, 9.6)	6.1 (3.9, 9.6)	6.4 (4.3, 10.0)	6.1 (4.3, 9.6)	6.8 (4.6, 11.1)
C-reactive protein (mg/L)	82 (37, 143)	94 (44, 165)	80 (33, 147)	80 (37, 141)	86 (42, 143)	65 (24, 131)
Mechanical ventilation	8,146 (6.5%)	748 (11%)	1,128 (6.3%)	3,433 (5.9%)	2,253 (6.6%)	584 (6.8%)
Non-invasive ventilation	3,386 (2.7%)	93 (1.4%)	263 (1.5%)	1,470 (2.5%)	1,357 (4.0%)	203 (2.4%)
Renal replacement therapy	1,326 (1.1%)	86 (1.3%)	189 (1.1%)	567 (1.0%)	326 (1.0%)	158 (1.8%)
Death/ discharge to hospice						
Alive	107,901 (86%)	5,559 (84%)	15,420 (86%)	50,634 (87%)	28,769 (84%)	7,519 (87%)
Death	14,321 (11%)	836 (13%)	1,876 (11%)	6,141 (11%)	4,624 (14%)	844 (9.8%)
Hospice	3,340 (2.7%)	240 (3.6%)	538 (3.0%)	1,528 (2.6%)	784 (2.3%)	250 (2.9%)

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156 **Table S16:** Sensitivity analysis of performance characteristics of m4C by pandemic wave using

157 only complete case records.

Cohort	AUC	Sensitivity	Specificity	PPV	NPV
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	Mean	95%CI	Mean	95%CI	Mean	95%CI	Mean	95%CI	Mean	95%CI
Overall	0.751	0.747 - 0.755	0.905	0.901 - 0.910	0.396	0.393 - 0.399	0.197	0.194 - 0.200	0.962	0.961 - 0.964
Wave 1	0.799	0.786 - 0.812	0.927	0.909 - 0.941	0.440	0.427 - 0.452	0.242	0.23 - 0.256	0.969	0.962 - 0.975
Wave 2	0.777	0.768 - 0.786	0.916	0.905 - 0.928	0.427	0.418 - 0.434	0.200	0.193 - 0.207	0.970	0.966 - 0.974
Wave 3	0.766	0.761 - 0.771	0.931	0.925 - 0.936	0.369	0.365 - 0.374	0.183	0.179 - 0.186	0.972	0.97 - 0.975
Delta	0.723	0.716 - 0.729	0.856	0.846 - 0.864	0.441	0.435 - 0.447	0.223	0.218 - 0.229	0.942	0.938 - 0.946
Early Omicron	0.734	0.719 - 0.750	0.931	0.916 - 0.945	0.311	0.301 - 0.321	0.164	0.155 - 0.173	0.969	0.961 - 0.975

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160 **Supplemental Figure Legends**

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162 **Figure S1:** Flowchart of cohort creation.

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164 **Figure S2:** Crude mortality rates stratified by m4C score in the entire cohort (“All waves”) and
165 by pandemic wave.

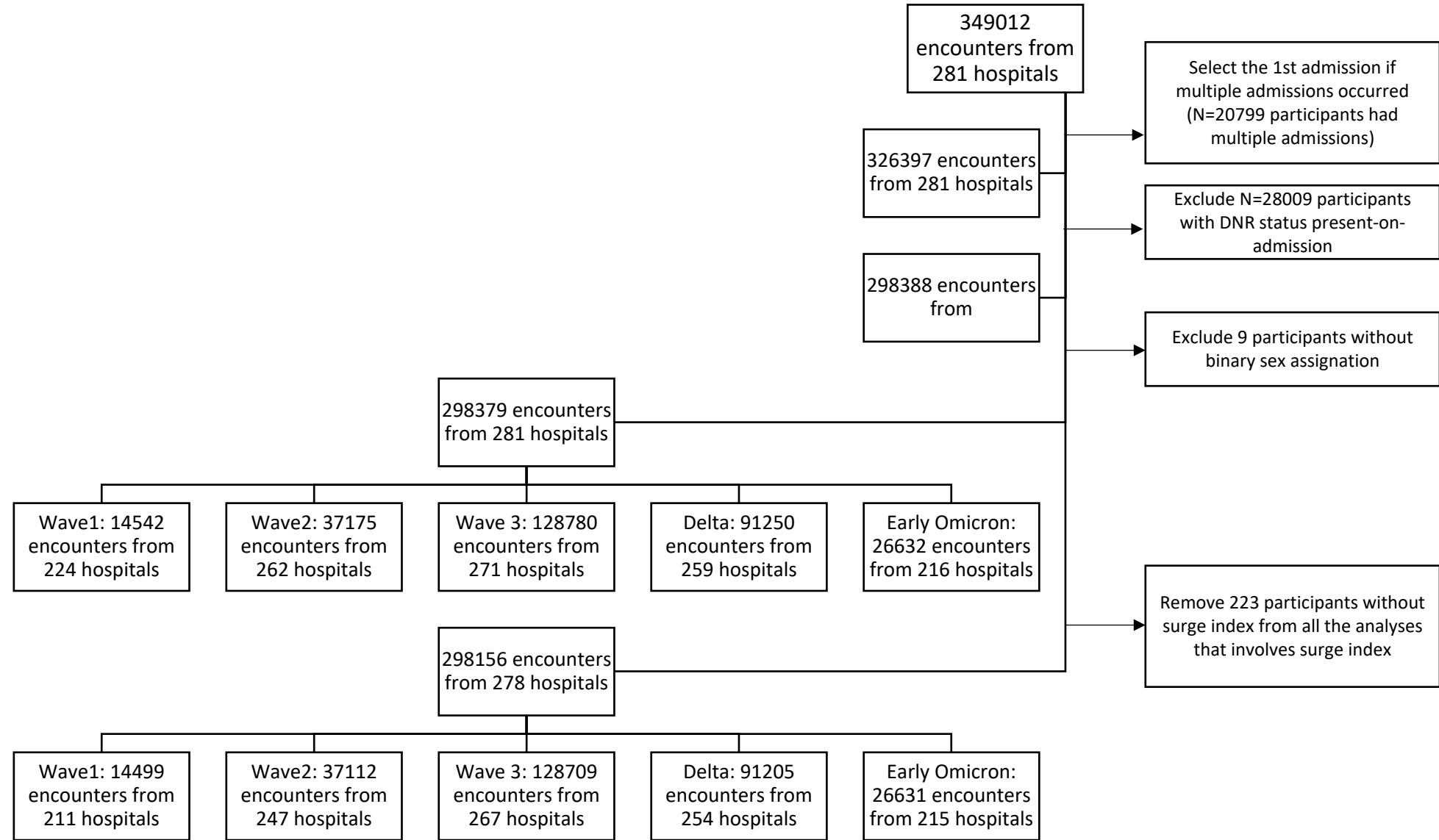
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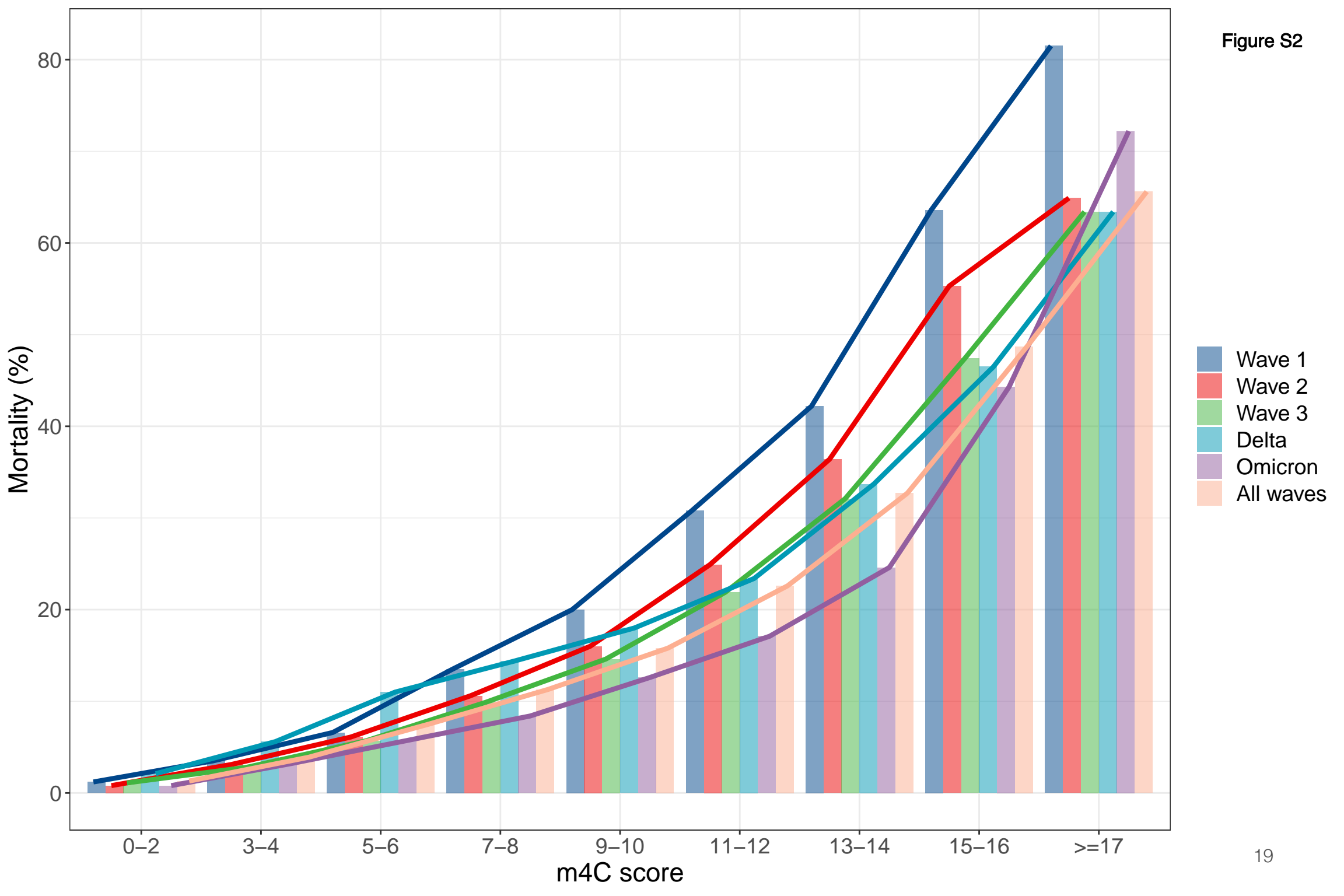
167 **Figure S3:** Calibration belts of m4C by pandemic wave, with models fit to data from Wave 1
168 (A), Wave 3 (B), and Delta (C). Solid lines represent relationship between predicted probability
169 and observed risk, shaded areas represent 95% confidence intervals. Dotted line represents ideal
170 calibration slope of 1 (bisector). Text indicates ranges of calibration belts lying under or over the
171 bisector.

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173 **Figure S4:** Calibration belts of m4C (“without surge”) and surge-adjusted models (“with surge”)
174 by pandemic wave. Solid lines represent relationship between predicted probability and observed
175 risk, shaded areas represent 95% confidence intervals. Dotted line represents ideal calibration
176 slope of 1.

Figure S1





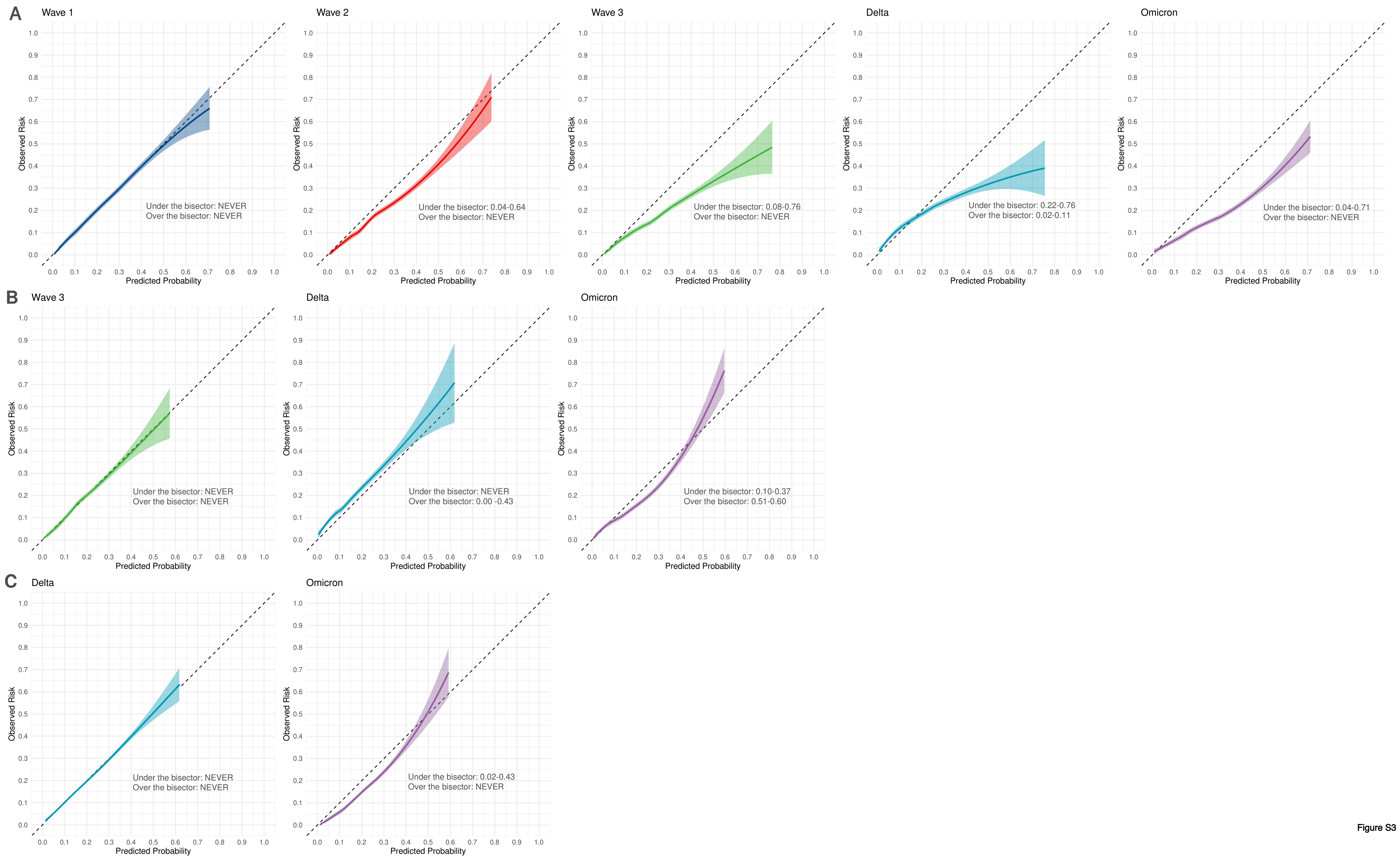
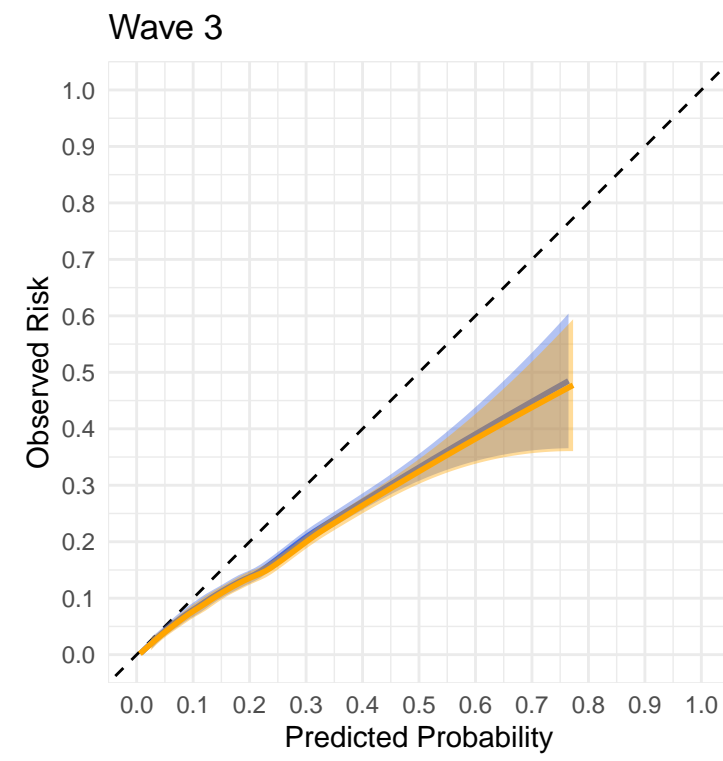
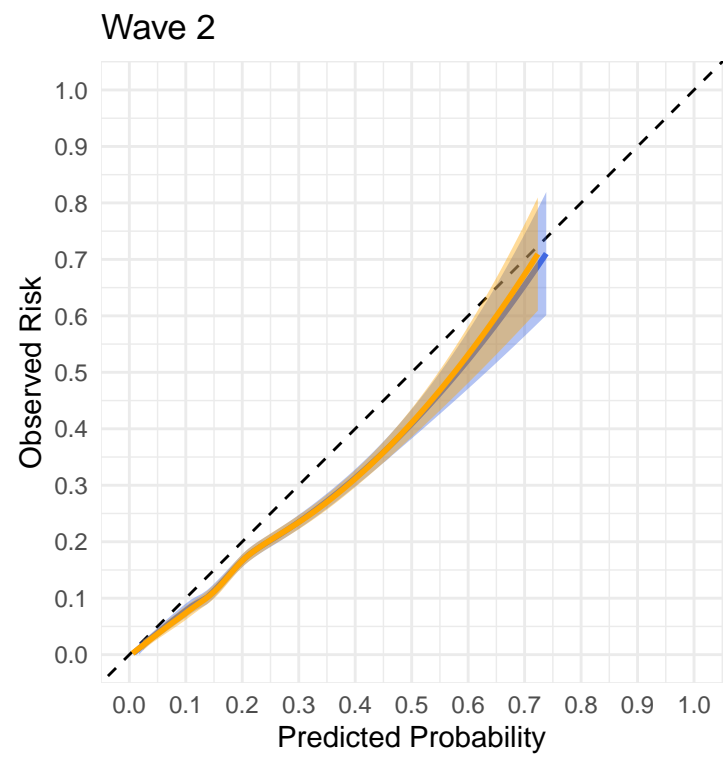
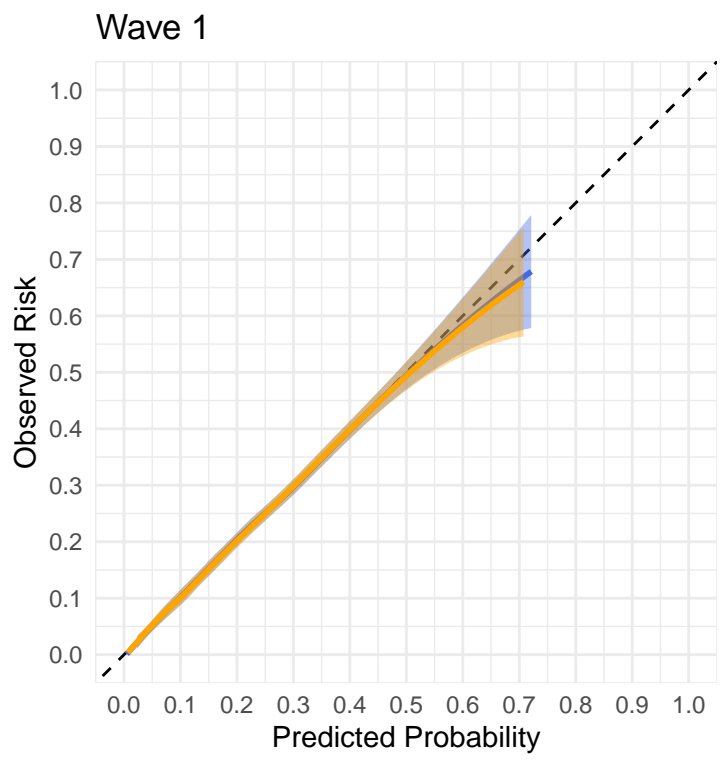


Figure S3



Models

- With Surge
- Without Surge

