

Establishment of Routine Clinical Indicators-Based Nomograms for Predicting the Mortality in Patients with COVID-19

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Research

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Abstract

Background: The aim of the study was to establish and validate nomograms to predict the mortality risk of patients with COVID-19 using routine clinical indicators.

Method: This retrospective study included a development cohort enrolled 2119 hospitalized COVID-19 patients and a validation cohort included 1504 COVID-19 patients. The demographics, clinical manifestations, vital signs and laboratory test results of the patients at admission and outcome of in-hospital death were recorded. The independent factors associated with death were identified by a forward stepwise multivariate logistic regression analysis and used to construct two prognostic nomograms. The models were then tested in an external dataset.

Results: Nomogram 1 is a full model included nine factors identified in the multivariate logistic regression and nomogram 2 is built by selecting four factors from nine to perform as a reduced model. Nomogram 1 and nomogram 2 established showed better performance in discrimination and calibration than the MuLBSTA score in training. In validation, Nomogram 1 performed better than nomogram 2 for calibration.

Conclusion: Nomograms we established performed better than the MuLBSTA score. We recommend the application of nomogram 1 in general hospital which provide robust prognostic performance but more cumbersome; nomogram 2 in mobile cabin hospitals which depend on less laboratory examinations and more convenient. Both nomograms can help clinicians in identifying patients at risk of death with routine clinical indicators at admission, which may reduce the overall mortality of COVID-19.

Introduction

With the continuing pandemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, there have been more than 50 million patients with coronavirus disease 2019 (COVID-19) globally and 1,286,063 deaths as of Nov 13, 2020 [1]. The clinical manifestations and outcomes of COVID-19 have been delineated in several studies, with 81% of patients presenting with subtle or minor symptoms, and 19% severe or critical cases [2]. Previous studies have reported that risk factors such as age, pre-existing comorbidities, and Neutrophil-to-lymphocyte ratio (NLR) were associated with higher mortality risk in COVID-19 [3–7]. A valid, ready-to-use predictive prognostic model at bedside for quick stratification of patients at risk of death are urgently need.

The MuLBSTA score [8], developed to assess the outcome of viral pneumonia, was reported to be associated with the outcome of COVID-19 in a few observational studies during the initial outbreak of COVID-19 in Wuhan (China) [9]. COVID-19 differed significantly from influenza A, rhinovirus, and other respiratory virus pneumonias that were used to build up the MuLBSTA score. Moreover, dichotomous classification of mortality risk as low or high risk, again, forced the clinician to make decision himself for the priority of medical resource when large number of patients are classified in the same group, which in turn minimize the usefulness of model prediction. Nomogram is a good method for this purpose with visualized interface and consecutive risk prediction. To date there are three studies of nomograms in

predicting death risk of COVID-19 [10–11]. The nomograms developed from those studies provided useful tools for researchers and clinicians in stratifying COVID-19 patients. However, the size of participants enrolled were limited in all three studies, and a lack of independent validation was noted in one study [10]. Furthermore, factors such as troponin (TNI), lactate dehydrogenase (LDH) included are not routine laboratory tests, the application of the nomograms are not suitable in mobile cabin hospitals or emergency health care centers.

In this study, we aim to: (1) develop nomograms with routine clinical indicators to predict the risk of death using 2119 cases of confirmed COVID-19; (2) compare the predictive efficacy of the nomograms with the MuLBSTA score; (3) assess the nomograms in an external validation cohort comprising 1507 cases.

Methods

Study design and participant

This retrospective study included a training cohort before tested in a validation cohort. Within 10 days, from Jan 22, 2020 to Feb 2, 2020, an emergency hospital with 1,000 beds named Huo-Shen-Shan (HSS) hospital was built in Wuhan (Hubei Province, China) by the Chinese government to admit confirmed COVID-19 patients. In the training cohort, patients admitted to HSS Hospital from Feb 4, 2020, to Mar 31, 2020, were retrospectively screened and were followed up to April 15, 2020, when the HSS Hospital closed. A validation cohort included COVID-19 patients admitted to Jin Yin-tan Hospital (Wuhan City, China) from Jan 26, 2020, to Feb 1, 2020 and COVID-19 patients admitted to Taikang Tongji Hospital (Wuhan City, China) from Feb 19, 2020, to Apr 2, 2020. In this way, we almost covered the whole spectrum of time from the COVID-19 outbreak to remission in Wuhan in validation cohort to ensure the data are representative. The study followed the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) checklist, and was approved by the ethics committee of Xinqiao Hospital (2020-yd073-01) with written informed consent waived due to the retrospective nature of the study.

Inclusion and exclusion criteria

Inclusion criteria

Patients diagnosed according to the World Health Organization (WHO) interim guidance for COVID-19 were included in the study [13].

Exclusion criteria

(1) Suspected cases of COVID-19; (2) sudden death following admission; (3) missing data; (4) duplications due to readmission or in-hospital transfer between wards.

Procedure and data collection

Eligible patients were enrolled and categorized into two groups according to the outcome of in-hospital death. The enrolment flow chart is shown in Fig. 1. The electronic medical records, nursing records, and laboratory tests of included patients were reviewed by a team consisting of experienced clinicians and statisticians. The dates of admission, discharge, and death were recorded and cross-checked. We collected data on age, sex, pre-existing comorbidities (hypertension, diabetes, cardiovascular diseases, chronic lung diseases, liver diseases), symptoms from onset to hospital admission (fever, cough, sputum, dyspnea, chest tightness, hemoptysis, fatigue, nausea, abdominalgia, diarrhea, anorexia), the duration time for initial symptoms, vital signs at hospital admission (body temperature, breathing rate, heart rate, blood pressure), and basic laboratory values on admission (white blood cell [WBC], neutrophil count, lymphocyte count, hemoglobin [Hg], platelet count [PLT], total bilirubin [TB], alanine aminotransferase [ALT], aspartate aminotransferase [AST], albumin [ALB], C-reactive protein [CRP], creatinine, creatine phosphokinase isoenzyme [CK-MB], IL-6 [interleukin 6], PCT [procalcitonin], and ESR [erythrocyte sedimentation rate]). The above laboratory tests were carried out in approved labs. The MuLBSTA score for each subject was calculated by two investigators (EL and JH) as reported previously [8]. When disagreement occurred, a senior investigator (SY) decided the final result.

Statistical analysis

Variables with missing data over 20% (IL-6, ERS and PCT, etc) were not included for further statistical analysis. Detailed information about missing data are reported in sTable 1 in the supplement. The remaining items were actually routine clinical indexes, and the proportion of observation with missing data was less than 12%. We employed mean substitution for imputation and completed some of the missing data by follow-up with a phone call. Continuous variables were expressed as the median (interquartile range [IQR]) or mean \pm SD, and categorical variables were presented as n (%). The differences in demographical, clinical characteristics and laboratory values between survivors and nonsurvivors were compared using Mann-Whitney U test, t test, Chi-Squared test, or Fisher's exact test as appropriate. Predictors with P-values less than 0.05 were fed to a forward stepwise multivariate logistic regression models to identify the independent candidate variables associated with COVID-19 fatality. The factors finally included to construct a nomogram were determined by both statistical significance and clinical values. To assess the discrimination of established nomograms, the area under the receiver operating characteristic curve (AUC) were measured. A calibration curve was generated for the evaluation of calibration, and judged with the Hosmer-Lemeshow test [14]. The clinical usefulness of the established score was evaluated with decision curve analysis (DCA) by assessing net benefits at various threshold probabilities [15]. In addition, the performance of the MuLBSTA score was also evaluated using the same methods described above, and the optimal cut-off value for the MuLBSTA score was adjusted according to Youden's index. Statistical analyses were performed using IBM SPSS 23 statistics software (SPSS Inc., Chicago, IL, United States) and R software (version 3.4, R Foundation, Vienna, Austria. [www. R-project.org](http://www.R-project.org)). All P-values were two-sided, and $P < 0.05$ was considered statistically significant.

Results

Characteristics of the training and validation cohorts

In total, 2271 COVID-19 cases were screened from HSS Hospital, among which 2119 cases were included as a training set according to the inclusion and exclusion criteria. 92 COVID-19 cases from Jin Yin-tan hospital and 1412 cases from Taikang Tongji hospital were including as a validation cohort (Fig. 1). The characteristics of training and validation cohort were listed in the supplement (sTable 2). In comparing the training and validation cohort, majorities of symptoms and part of underlying diseases were similar; whereas most of the laboratory tests were different. The in-hospital mortality rate was 3.1% in training cohort and 2.0% in validation cohort.

Building nomogram prognostic models in training cohort

In univariate analysis, variables between survivors and non survivors were compared, P value less than 0.05 were chosen as potential factors associated with in-hospital death of COVID-19 (Table 1). Variables chosen above were put in a forward stepwise multivariate logistic regression analysis to explore the independent risk factors. We identified age, dyspnea, anorexia, neutrophil-to-lymphocyte ratio (NLR), PLT, AST, ALB, and CRP as independent risk factors associated with in-hospital mortality of COVID-19 (Table 2). We first built up a full model (nomogram 1, designated as Nomo1) with all the indicators above, the model performed well with good discrimination and calibration (see below); However, the clinical practicability of applying a model including nine variables is cumbersome. Thus, we constructed a reduced model (nomogram 2, designated as Nomo2) regarding the weight value, previous reports of significance as well as accessibility in clinic. To use the nomograms, a ruler ranging from 0 to 100 points was scaled on top, with independent prognostic factors array on the relevant axis below. First, a subject's age was converted to a score by drawing a straight line upward to the ruler on the top and gets the score related to age, the procedure was carried out for every covariate, and the final risk score was calculated by adding up the score of each item to estimate the probability of in-hospital death referring to the risk axis below (Fig. 2 and sFigure 1).

Table 1

Demographics, clinical characteristics, vital signs, Laboratory findings and MuLBSTA score between survivors and non-survivors with COVID-19 [n(%)/Median(25%-75%)/Mean \pm SD].

| | All(N = 2119) | Survivors(n = 2053) | death(n = 66) | P value |
|--------------------------------------|-------------------|---------------------|-------------------|---------|
| Male | 1083(51.1) | 1041(50.7) | 42(63.6) | 0.039 |
| Age | 61.0(50.0 ~ 68.0) | 60.0(50.0 ~ 68.0) | 69.5(62.0 ~ 78.0) | 0.000 |
| Fever | 1496(70.6) | 1455(70.9) | 41(62.1) | 0.125 |
| Fatigue | 1174(55.4) | 1129(55.0) | 45(68.2) | 0.034 |
| Respiratory symptoms | 1683(79.4) | 1625(79.2) | 58(87.9) | 0.084 |
| Cough | 1488(70.2) | 1440(70.1) | 48(72.7) | 0.651 |
| Sputum | 237(11.2) | 233(11.3) | 4(6.1) | 0.180 |
| Dyspnea | 651(29.0) | 573(27.9) | 42(63.6) | 0.000 |
| Chest tightness | 415(19.6) | 391(19.3) | 18(27.3) | 0.110 |
| Hemoptysis | 7(0.3) | 6(0.3) | 1(1.5) | 0.199 |
| Gastrointestinal symptoms | 684(32.3) | 652(31.8) | 32(48.5) | 0.004 |
| Vomit | 46(2.2) | 43(2.1) | 3(4.5) | 0.171 |
| Abdominal pain | 18(0.8) | 17(0.8) | 1(1.5) | 0.436 |
| Diarrhea | 100(4.7) | 97(4.7) | 3(4.5) | 1.000 |
| Anorexia | 584(27.6) | 553(26.9) | 31(47.0) | 0.000 |
| Duration for initial symptom lasting | 20(13.0 ~ 30.0) | 20(14.0 ~ 30.0) | 14.5(10.0 ~ 25.3) | 0.003 |
| Hypertension | 678(32.0) | 651(31.7) | 27(40.9) | 0.115 |
| Diabetes | 280(13.2) | 263(12.8) | 17(25.8) | 0.002 |
| Cardiovascular disease | 122(5.8) | 113(5.5) | 9(13.6) | 0.005 |
| Chronic lung diseases* | 106(5.0) | 95(4.6) | 11(16.7) | 0.000 |

Definition of abbreviations: WBC = White blood cells, NLR = Neutrophil to lymphocyte ratio, ALT = alanine aminotransferase, AST = aspartate aminotransferase, CRP = C reactive protein, CK-MB = Creatine kinase-MB

* including bronchitis, chronic obstructive pulmonary diseases, pulmonary tuberculosis, and lung tumors.

† including Hepatitis (A, B, C, D, E), cirrhosis, fatty liver, and liver tumors.

| | All(N = 2119) | Survivors(n = 2053) | death(n = 66) | P value |
|---------------------------------------|----------------------|----------------------|---------------------|---------|
| Liver diseases [†] | 64(3.0) | 62(3.0) | 2(3.0) | 1.000 |
| Body temperature (Mean ± SD) | 37.8 ± 1.04 | 37.8 ± 1.04 | 37.8 ± 1.14 | 0.831 |
| Respiratory rate, breaths per min | 20.0(19.0 ~ 22.0) | 20.0(19.0 ~ 21.0) | 22.0(20.0 ~ 26.0) | 0.000 |
| Heart rate, beats per min | 85.0(78.0 ~ 95.0) | 84.0(78.0 ~ 95.0) | 88.5(80.8 ~ 101.0) | 0.003 |
| SBP, mmHg | 129.0(120.0 ~ 140.0) | 129.0(120.0 ~ 140.0) | 131(119.8 ~ 149.0) | 0.250 |
| DBP, mmHg | 80.0(73.0 ~ 88.0) | 80.0(74.0 ~ 88.0) | 80.0(68.0 ~ 88.0) | 0.182 |
| WBC, ·10 ⁹ /L | 5.7(4.8 ~ 7.1) | 5.7(4.8 ~ 7.0) | 7.6(5.6 ~ 12.9) | 0.000 |
| Neutrophil count, ·10 ⁹ /L | 3.5(2.8 ~ 4.7) | 3.5(2.8 ~ 4.6) | 6.3(3.7 ~ 11.4) | 0.000 |
| Lymphocyte count, ·10 ⁹ /L | 1.5(1.1 ~ 1.9) | 1.5(1.1 ~ 1.9) | 0.8(0.5 ~ 1.3) | 0.000 |
| NLR | 2.4(1.7 ~ 3.5) | 2.4 (1.7 ~ 3.4) | 11.1(2.8 ~ 21.6) | 0.000 |
| Hemoglobin concentration, g/L | 124.0(113.0 ~ 135.0) | 124.0(113.8 ~ 135.0) | 115(102.3 ~ 131.0) | 0.001 |
| Platelet count, ·10 ⁹ /L | 226.0(183.0 ~ 279.0) | 227.0(185.0 ~ 279.0) | 191.0(88.5 ~ 265.3) | 0.000 |
| Total bilirubin concentration, μmol/L | 9.5(7.3 ~ 12.3) | 9.4(7.3 ~ 12.2) | 10.9(8.3 ~ 18.5) | 0.000 |
| ALT, IU/L | 24.1(15.0 ~ 38.9) | 24.1(15.0 ~ 38.8) | 25.7(15.9 ~ 42.9) | 0.486 |
| AST, IU/L | 19.9(15.7 ~ 27.1) | 19.8(15.7 ~ 26.6) | 27.5(17.5 ~ 47.2) | 0.000 |
| Albumin concentration, g/L | 37.5(34.6 ~ 40.1) | 37.6(34.7 ~ 40.2) | 31.8(28.0 ~ 35.1) | 0.000 |
| CRP,mg/L | 2.4(0.9 ~ 9.8) | 2.3 (0.9 ~ 8.7) | 53.2(6.5 ~ 140.5) | 0.000 |

Definition of abbreviations: WBC = White blood cells, NLR = Neutrophil to lymphocyte ratio, ALT = alanine aminotransferase, AST = aspartate aminotransferase, CRP = C reactive protein, CK-MB = Creatine kinase-MB

* including bronchitis, chronic obstructive pulmonary diseases, pulmonary tuberculosis, and lung tumors.

† including Hepatitis (A, B, C, D, E), cirrhosis, fatty liver, and liver tumors.

| | All(N = 2119) | Survivors(n = 2053) | death(n = 66) | P value |
|--|-------------------|---------------------|-------------------|---------|
| Serum creatinine concentration, $\mu\text{mol/L}$ | 64.5(55.0 ~ 75.7) | 64.3(55.0 ~ 75.3) | 68.7(55.9 ~ 87.8) | 0.021 |
| CK-MB concentration, IU/L | 9.1(7.0 ~ 13.6) | 9.0(7.0 ~ 13.3) | 113.9(8.7 ~ 22.7) | 0.000 |
| MuLBSTA score | 7.0(5.0 ~ 9.0) | 7.0(5.0 ~ 9.0) | 11.0(9.0 ~ 13.5) | 0.000 |
| Definition of abbreviations: WBC = White blood cells, NLR = Neutrophil to lymphocyte ratio, ALT = alanine aminotransferase, AST = aspartate aminotransferase, CRP = C reactive protein, CK-MB = Creatine kinase-MB | | | | |
| * including bronchitis, chronic obstructive pulmonary diseases, pulmonary tuberculosis, and lung tumors. | | | | |
| † including Hepatitis (A, B, C, D, E), cirrhosis, fatty liver, and liver tumors. | | | | |

Table 2
Multivariate logistic regression modes used to construct Nomo1 and Nomo2 (N = 2119)

| | | OR | OR 95% C-I | | P value |
|-------|----------|-------|-------------|-------------|---------|
| | | | lower limit | Upper limit | |
| Nomo1 | age | 1.043 | 1.017 | 1.071 | 0.001 |
| | Dyspnea | 3.306 | 1.806 | 6.052 | 0.000 |
| | Anorexia | 2.828 | 1.535 | 5.208 | 0.001 |
| | WBC | 1.114 | 1.040 | 1.192 | 0.002 |
| | NLR | 1.038 | 1.005 | 1.072 | 0.023 |
| | PLT | 0.994 | 0.990 | 0.998 | 0.001 |
| | AST | 1.006 | 1.002 | 1.011 | 0.004 |
| | Albumin | 0.898 | 0.843 | 0.958 | 0.001 |
| | CRP | 1.012 | 1.006 | 1.017 | 0.000 |
| Nomo2 | age | 1.064 | 1.038 | 1.091 | 0.000 |
| | Dyspnea | 3.682 | 2.066 | 6.564 | 0.000 |
| | NLR | 1.073 | 1.039 | 1.107 | 0.000 |
| | CRP | 1.015 | 1.010 | 1.020 | 0.000 |

Internal validation of nomogram and the comparison with MuLBSTA score

We first used AUC to compare the discrimination of the established nomograms and MuLBSTA score in predicting mortality of COVID-19. Both Nomo1 and Nomo2 performed better discrimination than MuLBSTA score ($AUC_{Nomo1} = 0.920$, 95% CI 0.882–0.957 vs $AUC_{MuLBSTA} = 0.814$, 95% CI 0.76–0.868, $P < 0.001$; $AUC_{Nomo2} = 0.896$, 95% CI 0.855–0.936 vs $AUC_{MuLBSTA} = 0.814$, 95% CI 0.76–0.868, $P = 0.001$) (sTable 3). A calibration curve showed high consistency between predicted survival probability and actual survival proportion in Nomo1 and Nomo2, better than the calibration curve of MuLBSTA score (Fig. 3). The generated curve of DCA indicated that employing the Nomo1 and Nomo2 to identify the patients with high risk of death would be advantageous over the MuLBSTA score (sFigure 2).

External validation of the nomogram

The predictive value of Nomo1 and Nomo2 was further validated in external datasets. The Nomo1 showed an AUC of 0.92 (95% CI 0.86–0.98) and Nomo2 showed AUC of 0.89 (95% CI 0.83–0.96) in validation cohort (Table 3). For calibration, Nomo1 showed better agreement of observed proportion of death with predicted one than Nomo2 presented. Overall, the DCA also showed Nomo1 is more benefit in predicting COVID-19 patient mortality than Nomo2 in validation cohort. (Fig. 4).

Table 3
Nomograms in predicting COVID-19 mortality with external datasets. (N = 1504)

| | N | AUC (95%CI) | Sen (%95%CI) | Spe (%95%CI) | Acc n(%95%CI) | Youden's index |
|-------|------|---------------------|------------------------|------------------------|------------------------|----------------|
| Nomo1 | 1504 | 0.92 (0.86–0.98) | 86.67 (74.50-98.83) | 88.74 (87.12–90.35) | 88.70 (87.10–90.30) | 0.75 |
| Nomo2 | 1504 | 0.89 (0.83–0.96) | 76.67 (61.53–91.80) | 89.82 (88.28–91.37) | 89.56 (88.02–91.11) | 0.66 |

Note: AUC = Area under the curve. Sen = Sensitivity. Spe = specificity. Acc = accuracy

Discussion

In this study, we identified nine routine clinical indexes, including age, dyspnea, anorexia, NLR, PLT, AST, ALB, and CRP as independent risk factors for COVID-19 fatality. Two predictive score nomograms were established based on the above variables to evaluate the mortality risk of COVID-19. Nomo1 and Nomo2 predicted mortality with a larger AUC than that for the MuLBSTA score in the training cohort, also with satisfactory AUC_{nomo1} of 0.92 (95% CI 0.86–0.98) and AUC_{nomo2} of 0.89 (95% CI 0.83–0.96) in external

validation cohort. To the best of our knowledge, this is the largest study with external validation aimed to construct nomograms that includes routine clinical indicators to predict COVID-19 mortality risk.

Age is an acknowledged risk factor associated with disease severity and prognosis of COVID-19 [16]. In our study, the median ages in survivors and non-survivors were 60.0(49.3 ~ 68.0) and 69.0(62.0 ~ 78.0), respectively. A retrospective study of 1099 COVID-19 patients carried out in China showed the median ages were 45.0 (34.0–57.0) in non-severe patients and 52.0 (40.0–65.0) in severe patients [5]. Mortality increased sharply to 7.8% in aged patients over 80, while the overall death rate was estimated to be 0.66% [17]. Similar results have been characterized in other studies [18]. Moreover, a study of 577 patients identified age over 60 as an independent prognostic factor for 12-day mortality [19].

Although within the normal range, in our study, WBC and neutrophil counts were significantly higher in non-survivors when admitted. We also noted lymphocytopenia in non-survivors. Lymphocytopenia had been reported as a characteristic of COVID-19 since the lymphocyte count in ICU patients was 0.4 (0.2–0.8) compared with 1.0 (0.7–1.1) in non-ICU patients [20]. Furthermore, lymphocyte count was integrated in a predictive model for COVID-19 fatality [21]. The net effect of elevated neutrophils and decreased lymphocytes resulted in raised NLR. In other studies, $NLR \geq 2.22$ had been used to recognize COVID-19, and $NLR \geq 4.06$ was an indicator of severe disease [22]. In our study, both WBC and NLR were identified as independent risk factors associated with COVID-19 mortality, we included NLR in the reduced model for the robustness of NLR used to predict mortality risk of COVID-19 in other study [11].

CRP is elevated in response to inflammatory disease to protect against infection, to clear damaged cells and to regulate the inflammatory response. In our study, the CRP was significantly elevated in nonsurvivors compared with survivors (52.38 (7.76 ~ 132.7) vs 2.46(0.92 ~ 10.07) mg/L). CRP is significantly elevated in deaths compared with recovered patients with severe diseases (113 [69.1-168.4] vs 26.2 [8.7–55.8]) in a retrospective study delineating the clinical characteristics of 113 nonsurvivors with COVID-19 [23].

Dyspnea is a symptom which can reflect the severity of the disease. Dyspnea has been reported to be associated with increased risk of developing ARDS in another study [24]. We observed that 18 (25.35%) non-survivors were common type when admitted, who reported symptoms of dyspnea but not respiratory distress, ahead of their subsequent disease progression into severe type. The involvement of dyspnea in the score compensates for underestimating death in patients in the early stage before disease progression.

PLT count was reported to be lower in severe COVID-19 patients [5]. In our study, we also found that PLT was lower in nonsurvivors compared with survivors (190 [87 ~ 265] vs. 227 [184 ~ 280], $p < 0.01$). However, PLT was reported to be significantly higher in ICU patients than in non-ICU patients [20], and the study carried out in Jin Yin-tan Hospital that enrolled 52 critically ill patients showed that the non-survivors had elevated PLT [25]. We speculate that the difference between studies may be influenced by selection bias and the number of patients enrolled. In our study, PLT is a protective factor for survival.

Gastrointestinal involvement has been observed in COVID-19 patients [26–27]. Anorexia was reported to be associated with ICU admission for the patients with COVID-19 [28]. In our study, anorexia is an independent predictor of death. Regarding liver function, AST and TB were higher while ALB was lower in non-survivors compared with survivors, but ALT was insignificant between the two groups. A meta-analysis including 35 studies of 6686 COVID-19 patients showed that the pooled prevalence of digestive system comorbidities was 4%, and the pooled prevalence of abnormal liver function was 19%. ALT, AST, and TB predicted severe cases with pooled ORs of 1.89 (1.30–2.76), 3.08 (2.14–4.42) and 1.39 (0.78–2.47), respectively [24].

The MuLBSTA score was previously used to predict the mortality risk of viral pneumonia. This model was established mainly by patients with influenza pneumonia and other viral pneumonias except for SARS-CoV-2 infection. Seven parameters, including multilobular infiltrates, lymphocytes, bacterial coinfection, acute smoker, former smoker, hypertension and age ≥ 60 years were included. It has been reported that the deaths with COVID-19 had high MuLBSTA scores [29]. In our study, non-survivors had higher MuLBSTA scores than survivors (11[7 ~ 13] vs 7[5 ~ 9], $P < 0.001$). Although the MuLBSTA score was higher in non-survivors, the AUC of the MuLBSTA score was 0.814 (95% CI 0.76–0.868), with a sensitivity of 40.91% (28.79–53.03%). The poor sensitivity of the MuLBSTA score made it unsuitable for prediction of death. By adjusting the optimal cut-off value from the reported 12 to 10.5 according to the Youden Index, the sensitivity of the MuLBSTA score increased to 66.67% (95% CI 54.55%-77.27%). Compared with the MuLBSTA score, besides the advantages of our model in discrimination and calibration, our models calculated individualized death probability rather than assigning cases into low or high-risk groups.

The present study has several advantages. First, the study has a large sample size, recruiting patients from late January to early April, representative of the COVID-19 epidemic in Wuhan, China. Second, all variables included in the nomogram are routine clinical indexes, making it applicable in most medical institutions worldwide. Third, two nomograms were built for different purpose, Nomo1 is more robust and Nomo2 is more convenient, clinician may choose either one appropriate according to the situation.

This study also has some limitations. First, it is a retrospective study, bias is inevitable, the results should be interpreted carefully as an exploratory study. Second, since the study was carried out in a single city (Wuhan, China), the results are not fully representative. The predictive potency of the nomogram needs to be verified in other medical facilities outside of Wuhan. However, despite these limitations, we have successfully identified in-hospital mortality risk factors of COVID-19 and have constructed predictive nomograms to estimate the in-hospital mortality risk of COVID-19 based on routine clinical indicators.

Conclusion

Nomograms we established performed better than the MuLBSTA score. We recommend the application of Nomo 1 in general hospital which provide robust prognostic performance but more cumbersome; Nomo 2 in mobile cabin hospitals which depend on less laboratory examinations and more convenient.

Both nomograms can help clinicians in identifying patients at risk of death with routine clinical indicators at admission, which may reduce the overall mortality of COVID-19.

Declarations

Ethical Approval and Consent to participate

Ethical approval was obtained from the ethics committee of Xinqiao Hospital (2020-yd073-01) with written informed consent waived due to the retrospective nature of the study.

Consent for publication

Not applicable.

Availability of supporting data

Data are not collected from a public database. All relevant data are available upon request from the corresponding author

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Dr. Shiming Yang and Dr. Yu Xu had full access to all of the data in the study and are responsible for the authenticity and accuracy of the data manipulation and analysis. Dr. Mingdong Hu contributed equally to this work.

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Figures

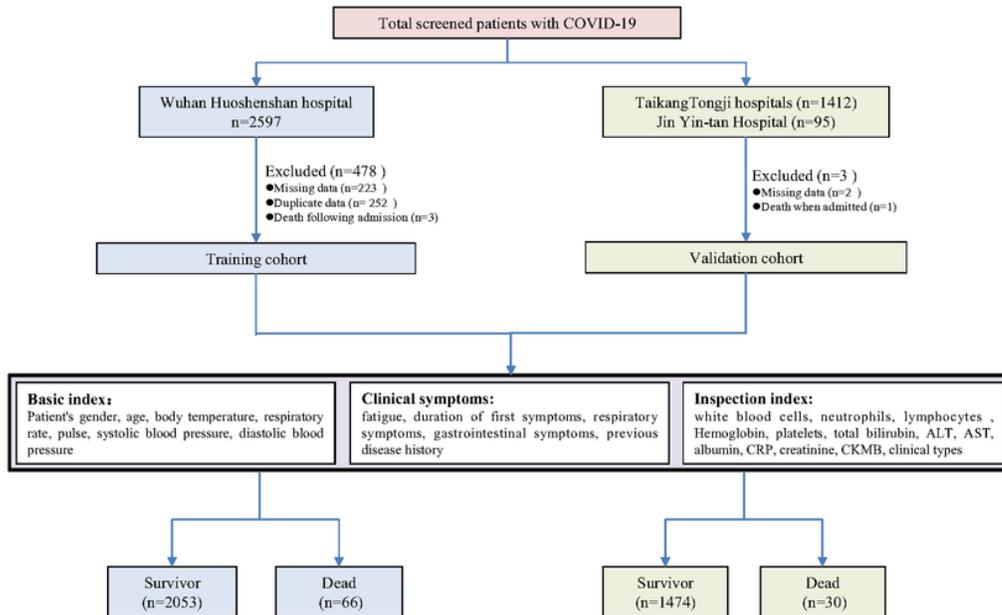


Figure 1

Enrolment flow chart of study population in training and validation cohorts.

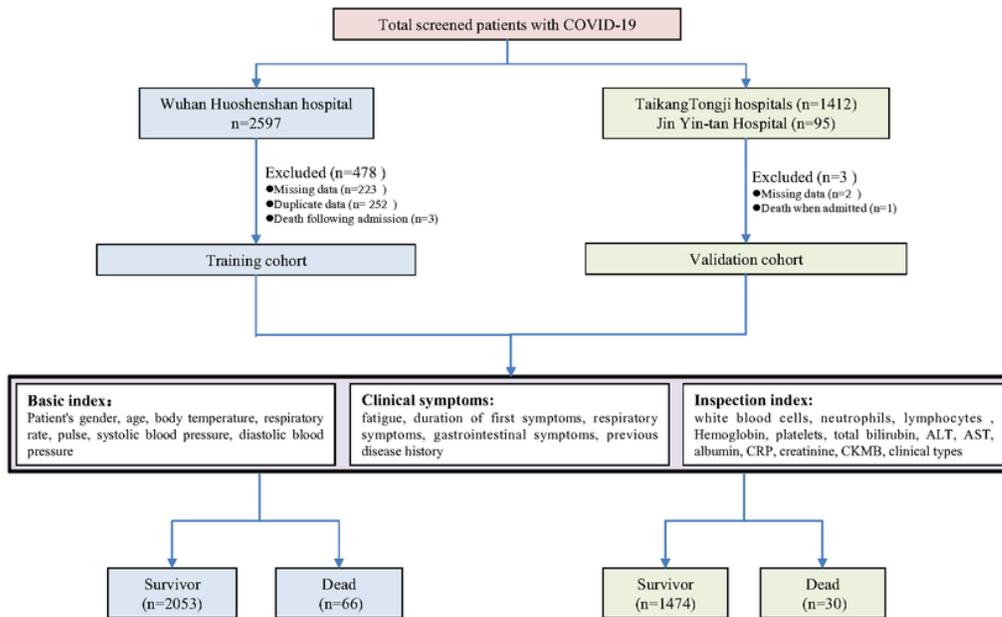


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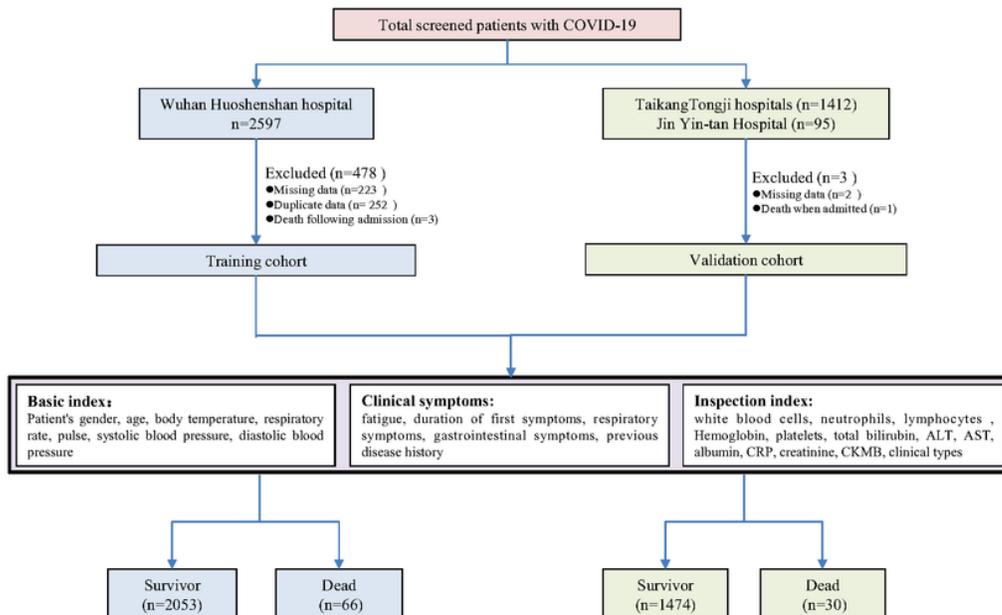


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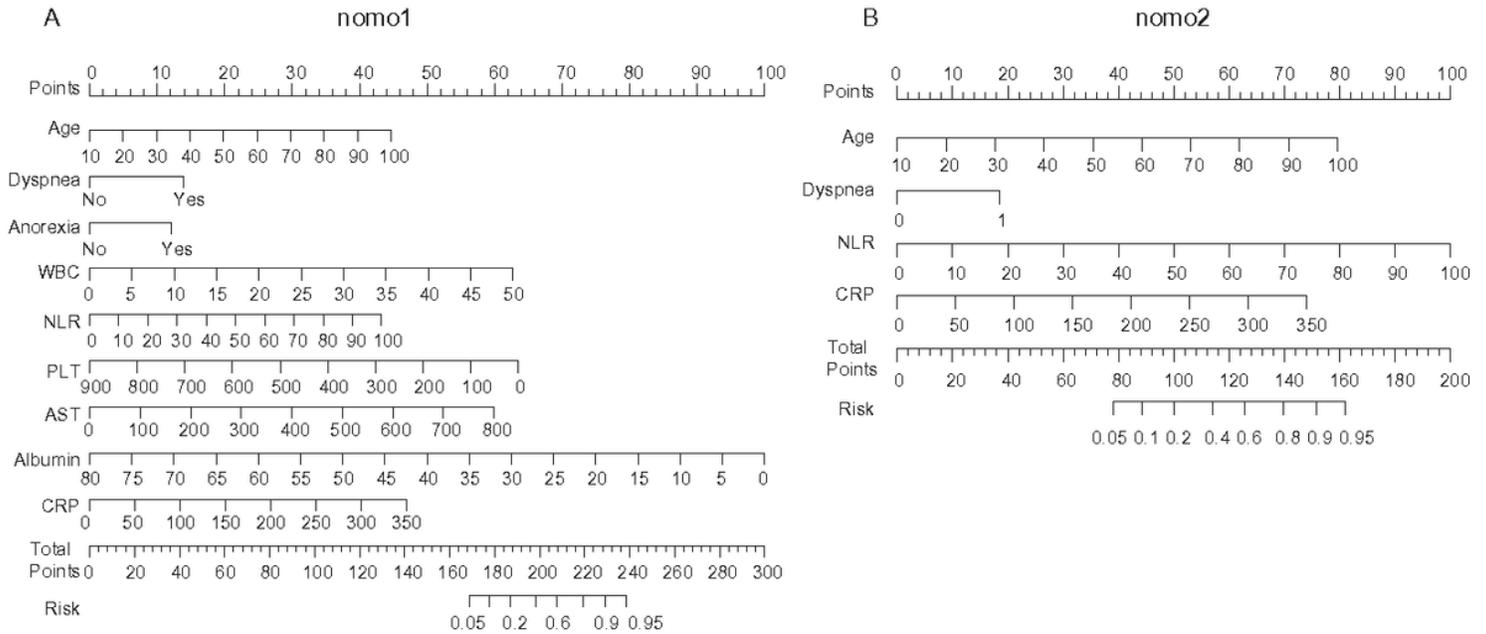


Figure 2

Establishing nomograms with identified risk factors. (A) Nomo1 was established by including nine identified independent risk factors. (B) Nomo2 was established by including age, dyspnea, NLR, and CRP.

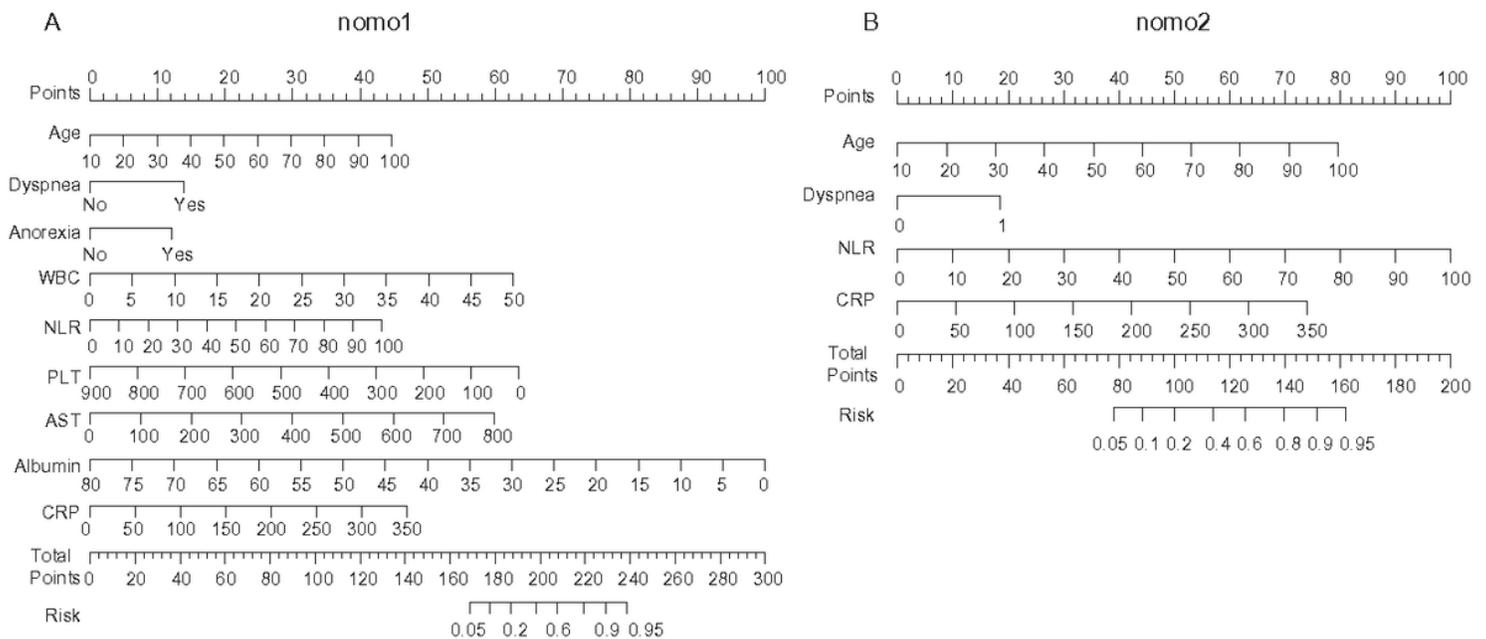


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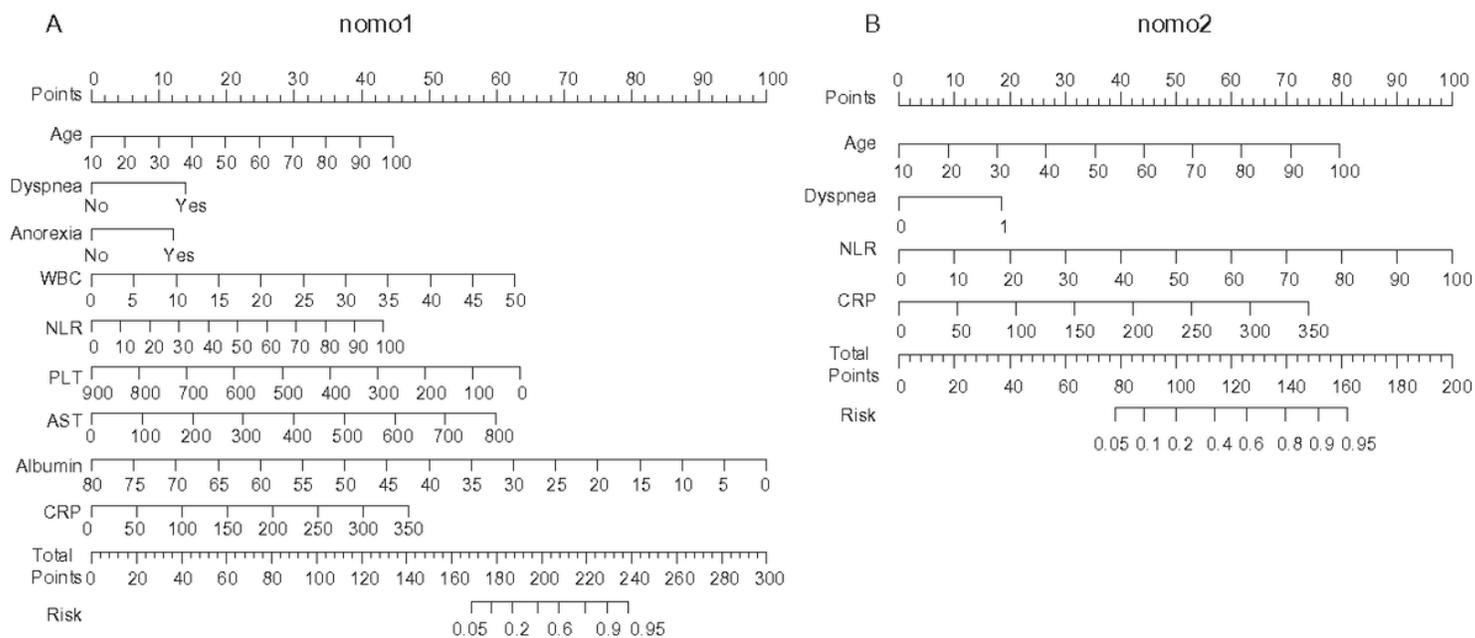


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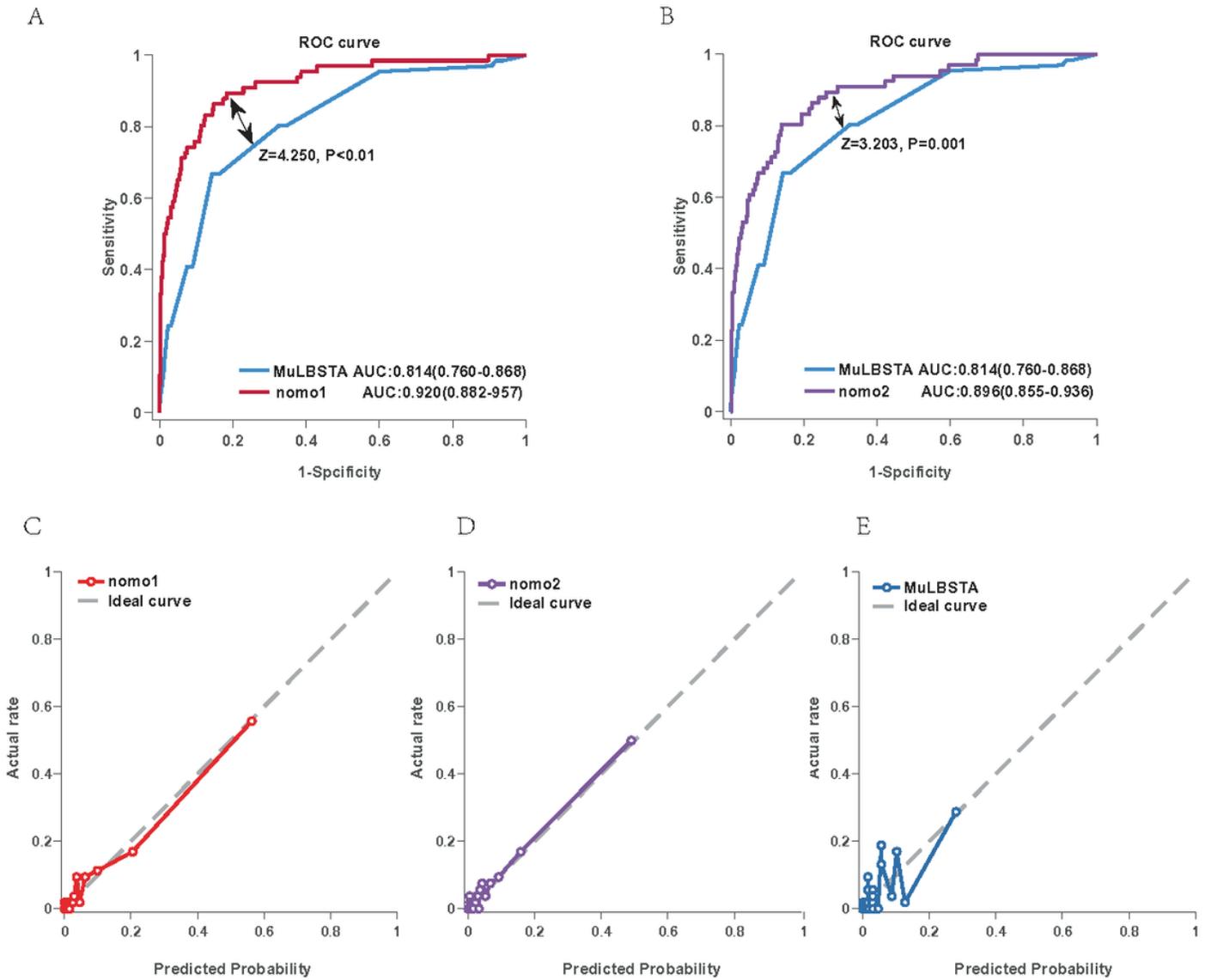


Figure 3

The performance of the Nomo1, Nomo2 and the MuLBSTA score in predicting mortality of COVID-19 in training cohort. AUC curve analyses were generated to test the discrimination of Nomo1 and the MuLBSTA score (A) or Nomo2 and the MuLBSTA score (B). Calibration curves were generated for Nomo1 (C), Nomo2 (D), and the MuLBSTA score (E). The dashed line represents an ideal prediction.

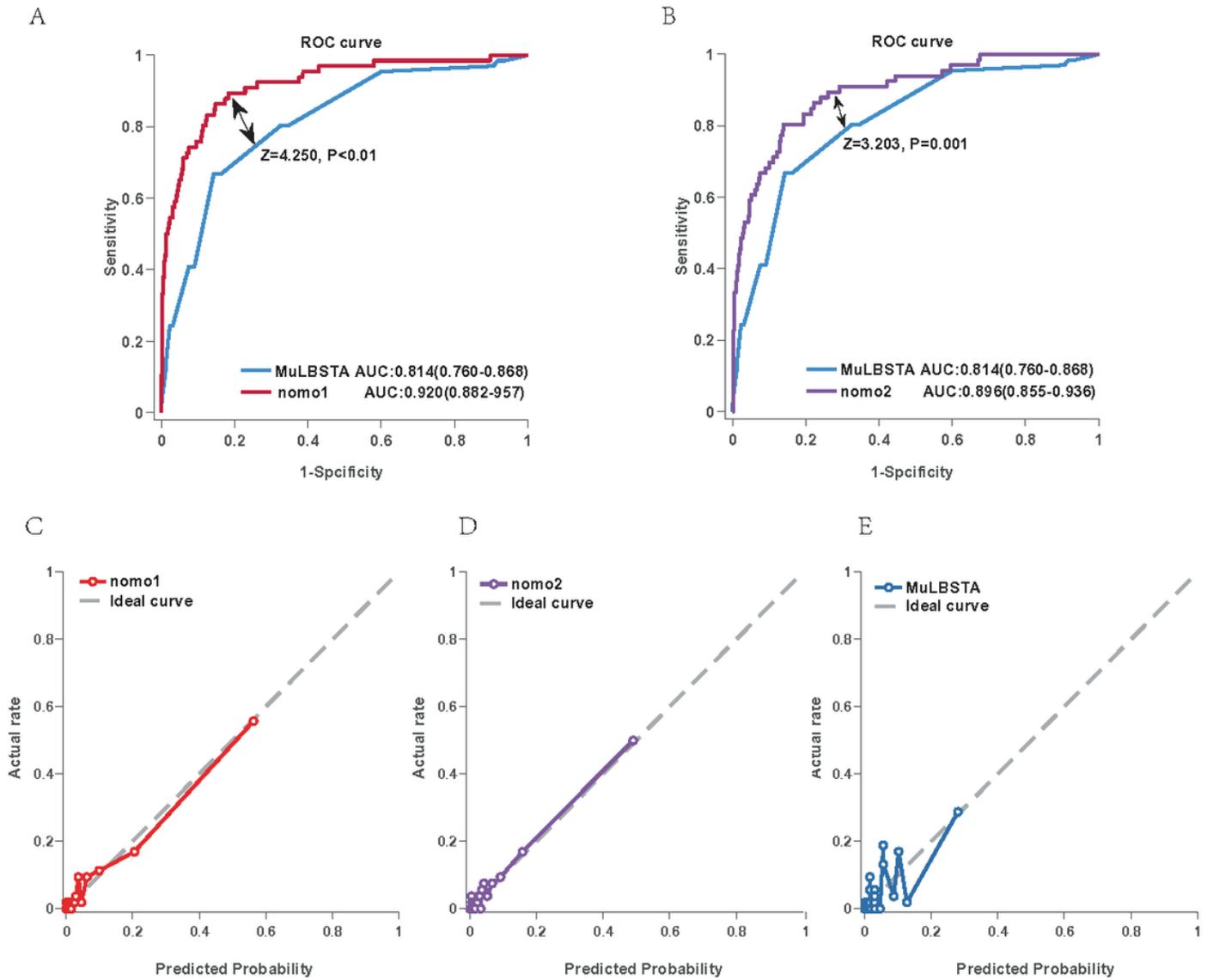


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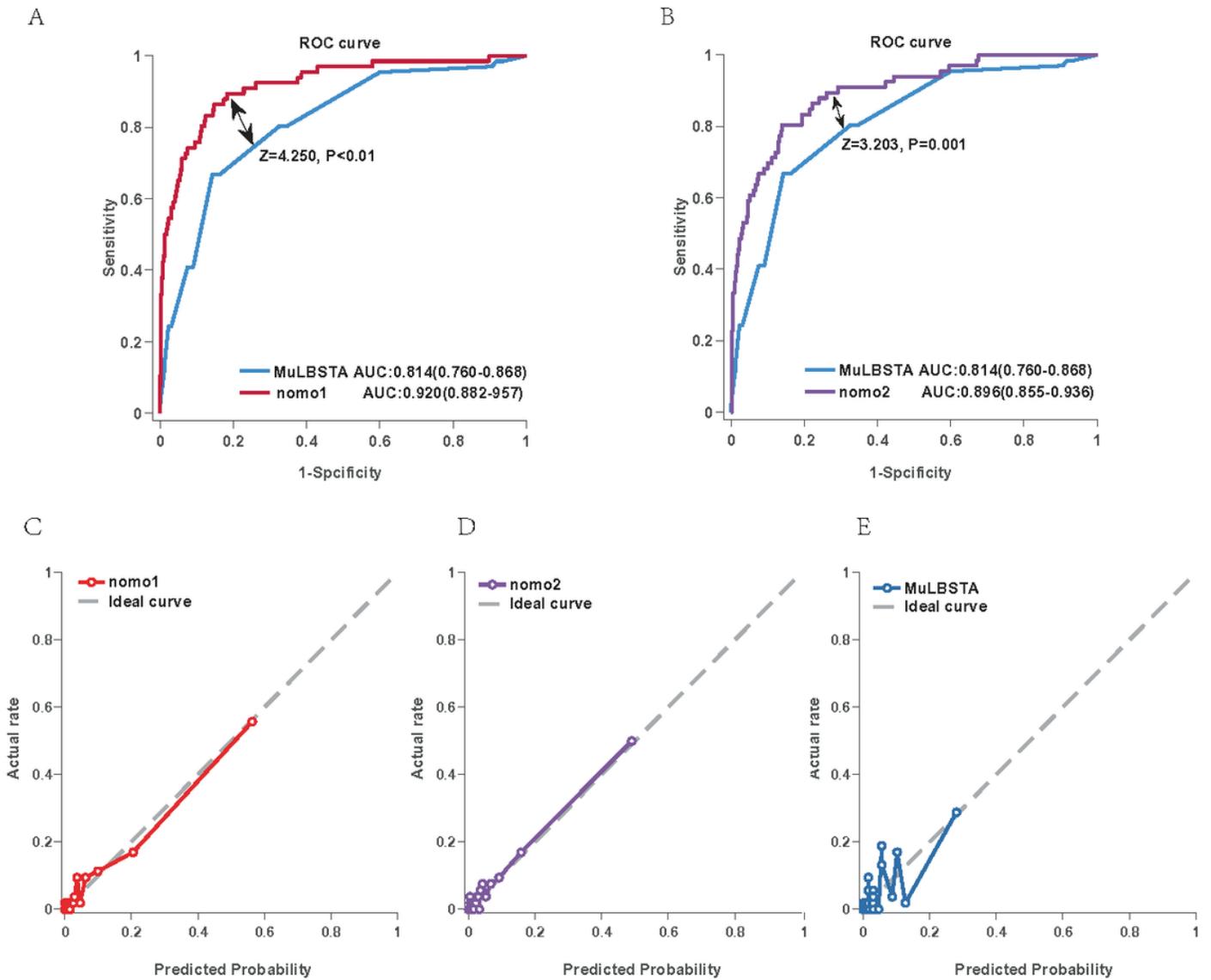


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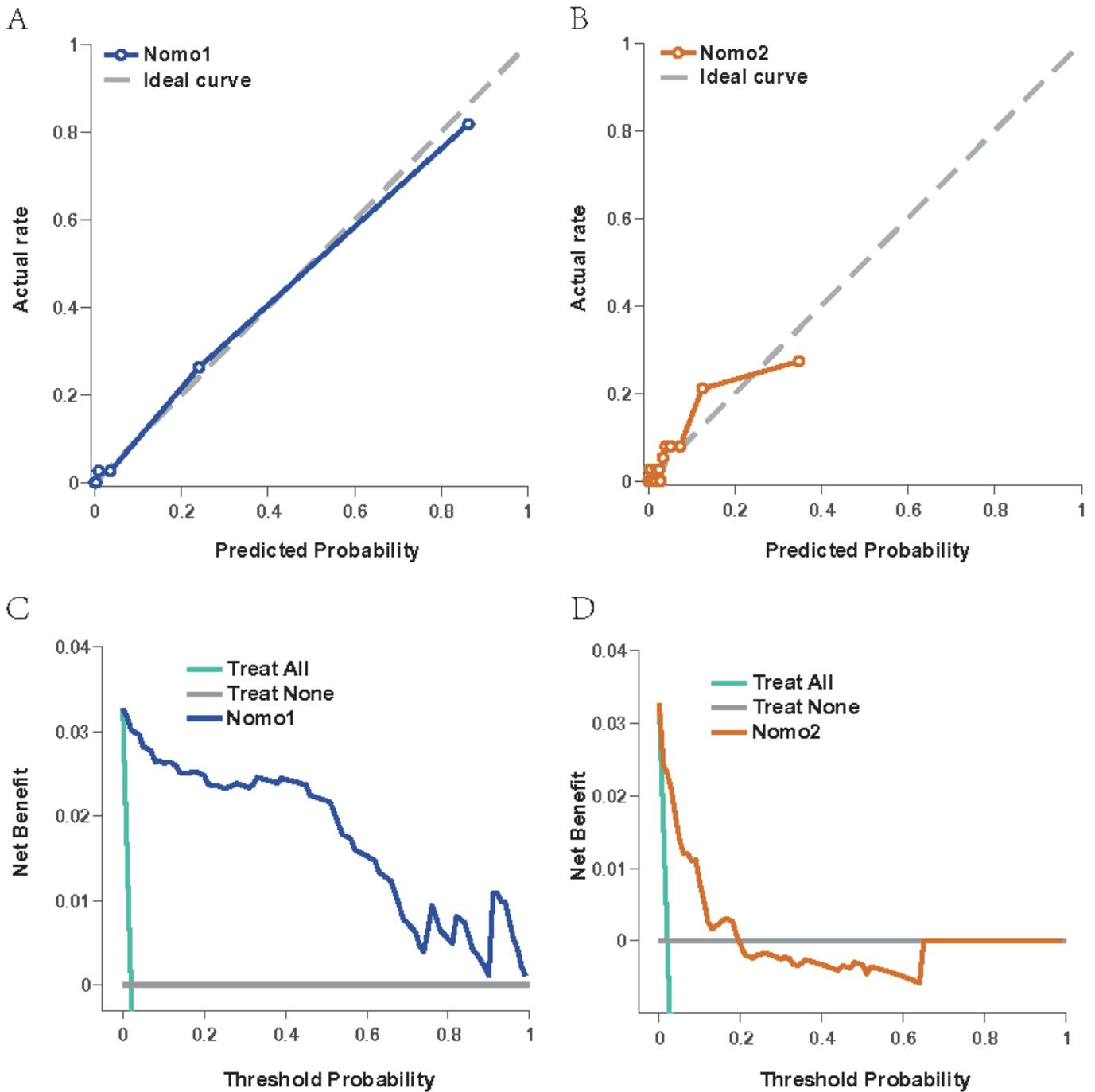


Figure 4

Nomo1 and Nomo2 in predicting mortality of COVID-19 in validation cohort. Calibration curves for Nomo1 (A) and Nomo2 (B). Decision curve analysis for Nomo1 (C) and Nomo2 (D)

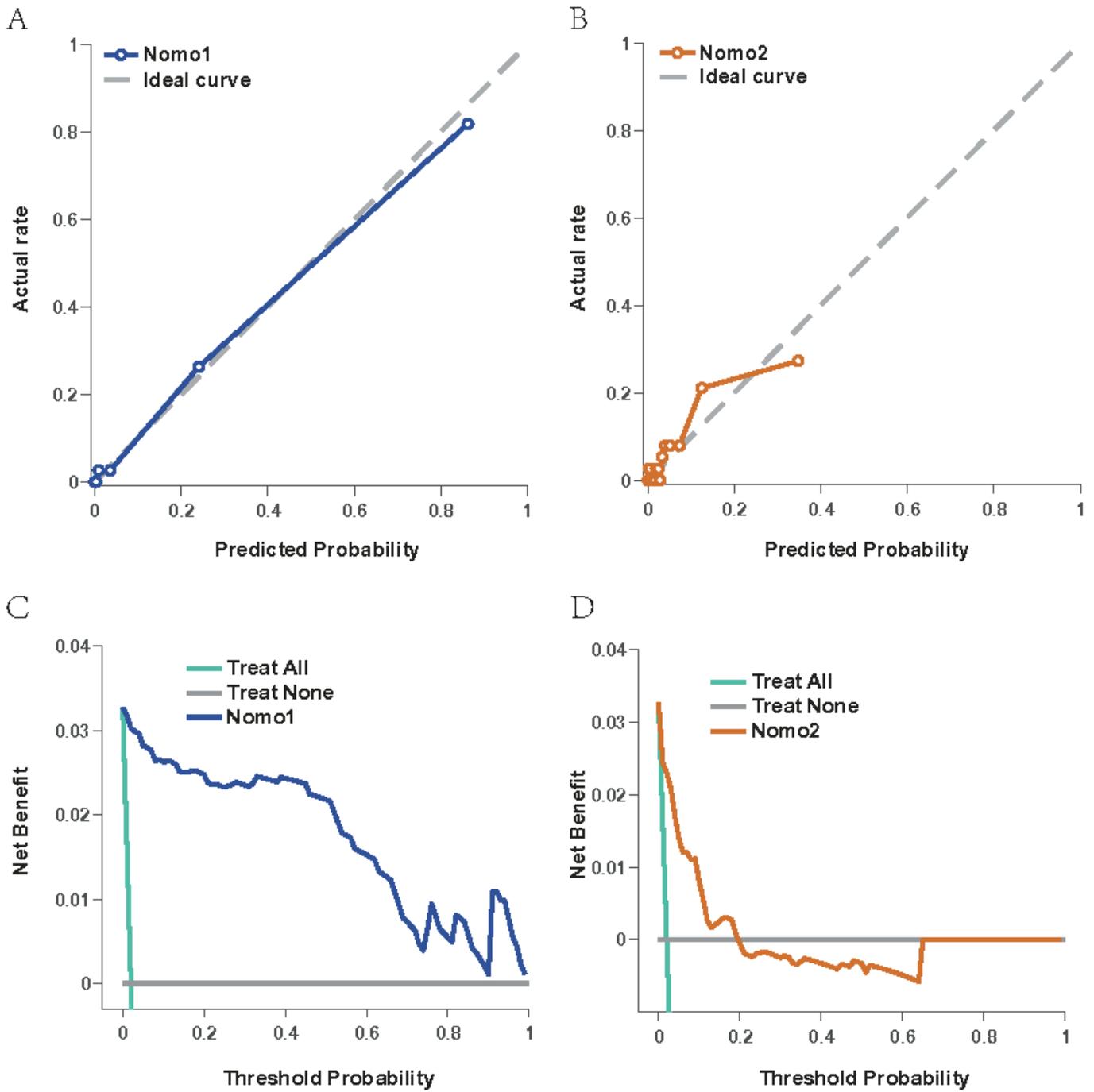


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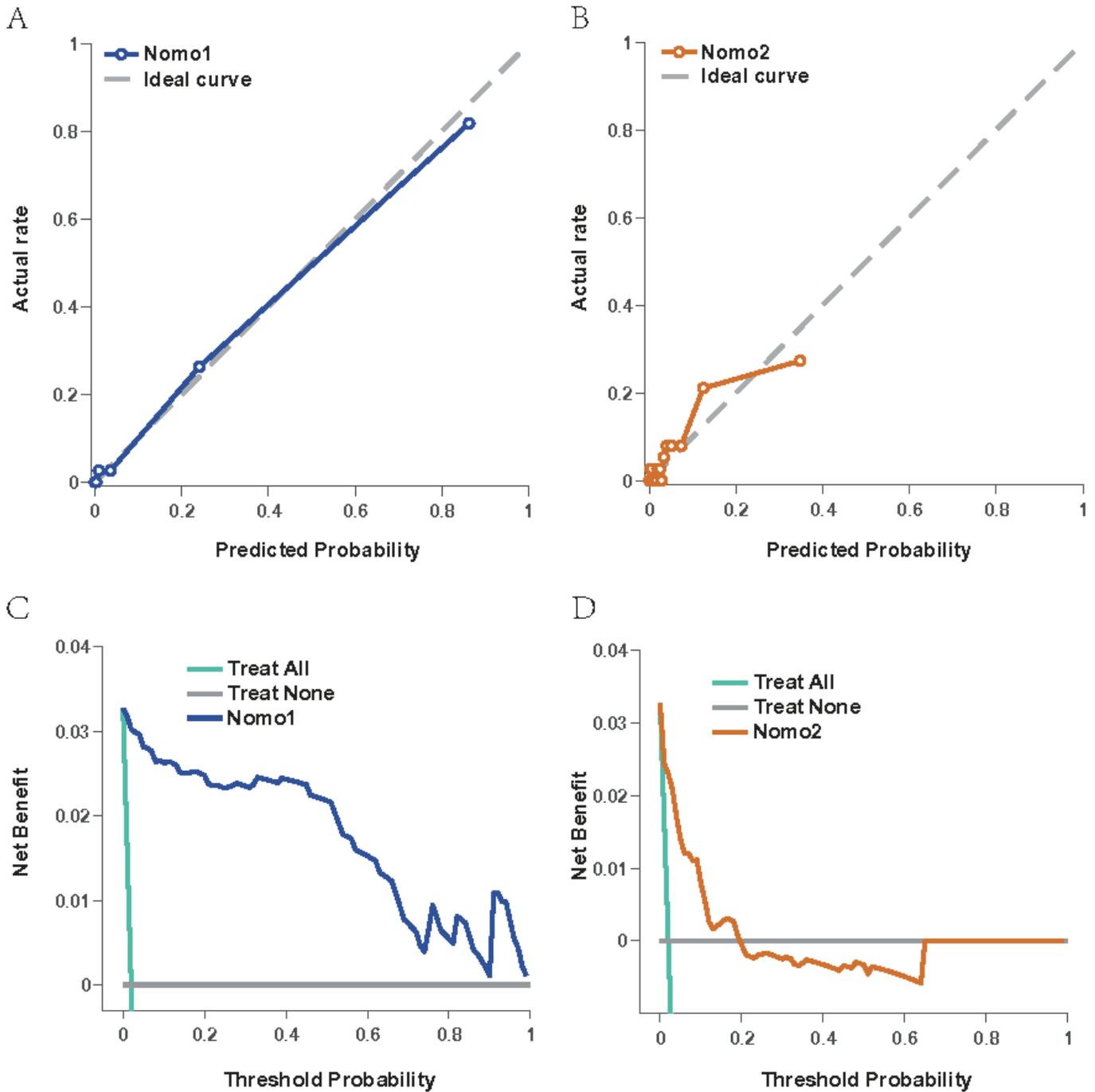


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