

**Full Title: Derivation and validation of a novel prognostic scale
(modified-SOAR) to predict early mortality in acute stroke**

Cover Title: Modified-SOAR score and early mortality

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ABSTRACT:

Background and Purpose: The SOAR stroke score (stroke Subtype, Oxfordshire Community Stroke Project classification, Age and pre-stroke modified Rankin scale) is a prognostic scale proposed for early mortality prediction following acute stroke. We aimed to evaluate whether including a measure of initial stroke severity (National Institutes of Health Stroke Scale [NIHSS], a modified-SOAR (mSOAR)), would improve the prognostic accuracy.

Methods: Using Anglia Stroke & Heart Clinical Network data, 2008-2011, we assessed performance of SOAR and mSOAR against in-hospital mortality using area under the receiver operating curve (AUROC) statistics. We externally validated the prognostic utility of SOAR and mSOAR using an independent cohort dataset from Glasgow. We described calibration using Hosmer-Lemeshow goodness-of-fit test.

Results: A total of 1002 patients were included in the derivation cohort, 105 (10.5%) died as in-patient. The AUROCs for outcome of early mortality derived from the SOAR and mSOAR were: 0.79 (95% confidence intervals [95%CI], 0.75-0.84) and 0.83 (95%CI: 0.79-0.86), respectively, ($p=0.001$). The external validation dataset contained 1012 patients with stroke, of which 121 (12.0%) patients died within 90 days. The mSOAR scores identified risk of early mortality ranging from 3% to 42%. External validation of mSOAR yielded AUROC of 0.84 (95%CI: 0.82-0.88) for outcome of early mortality. Calibration was good ($p=0.70$ for the Hosmer-Lemeshow test).

Conclusions: Adding NIHSS data to create a modified-SOAR score improved prognostic utility in both derivation and validation datasets. The mSOAR may have clinical utility by using easily available data to predict mortality.

INTRODUCTION:

There are a growing number of prognostic models and scales designed to predict mortality or other outcomes following acute stroke.¹⁻⁸ Although many of the scales have favorable properties reported, few have been incorporated into routine clinical practice. Two common limitations in prognosis research are failure to modify scales with new covariates that may improve performance and lack of external validation of scales in independent cohorts.⁹

The SOAR stroke score (stroke subtype [ischemic or hemorrhagic], Oxfordshire Community Stroke Project classification, age and pre-stroke modified Rankin scale) was recently proposed for early mortality prediction following an acute stroke.^{10, 11} The score may potentially be clinically useful due to its simplicity, with uncomplicated scoring rules and use of readily available data. Although, the prognostic accuracy of SOAR score in the original description was reasonable,^{10, 11} there was scope to improve further. The major limitation of SOAR is the lack of consideration of acute stroke severity marker. The best predictive values possible are needed to avoid giving patients and family wrong and potentially damaging prognostic information. An initial acute stroke severity score, National Institutes of Health Stroke Scale (NIHSS) on admission, is well established as an independent predictor of outcome post-stroke.¹²⁻¹⁴ Furthermore, the usefulness of SOAR beyond in-patient stay is not examined previously.

In this paper, we aimed to evaluate whether including a measure of initial stroke severity (National Institutes of Health Stroke Scale [NIHSS]) to form a modified SOAR (mSOAR) score, would improve the prognostic accuracy and also assessed this would be applicable up to 90-days post stroke in an independent dataset.

METHODS

The SOAR score

The description for the original SOAR score's derivation has been published elsewhere.¹¹

Briefly, the SOAR score is an 8-point scale (0-7) (Table 1). The total SOAR score is the sum of points allocated for each of the input variables, all measured at the time of admission.

Derivation of modified-SOAR score (mSOAR)

Data Source: We conducted a retrospective analysis on routine clinical database held as part of the Anglia Stroke & Heart Clinical Network (ASHCN), which recorded consecutive stroke admissions between 2008 and 2011 and followed till hospital discharge. The registry is in a geographical area of England and includes eight National Health Service (NHS) hospitals in Norfolk, Suffolk and Cambridgeshire. Of note, most in-hospital deaths in ASHCN occurred within 90-day; 81% of within 90 days deaths were in-hospital deaths in Anglia Stroke Network Evaluation Study (ASCNES)¹⁵ the participants of which were drawn from ASHCN database.

All patients included were confirmed stroke cases aged 18 years and over based on expert multidisciplinary clinical assessment informed by neuroimaging and other investigations as per usual clinical practice. All included patients were treated as per institutional practice and stroke guidelines. Relevant Institutional & Ethical approvals of use of ASHCN data was obtained as part of ASCNES.¹⁵ Conduct and reporting of our analysis is in accordance with the UK Medical Research Council (MRC) PROgnosis RESearch Strategy (PROGRESS) Partnership best practice guidance.¹⁶

Participants and variables

We included patients for whom we had baseline demographic and outcome information to designate our prognostic scales and chosen outcome. Variables included to calculate SOAR

and mSOAR scales were: age (years), stroke subtype (ischemic or hemorrhagic, based on clinical and neuroimaging finding), OCSP classification (total or partial anterior circulation, posterior circulation or lacunar strokes), pre-stroke mRS and baseline NIHSS at the time of first assessment on hospital arrival. Outcome of interest was all cause mortality censored at discharge. The length-of-stay for individuals who lived was a median of 9 (interquartile range, IQR 5-19) days; and for those who died; 10 (IQR 5-27) days.

External validation

We validated mSOAR score performance using pooled data from two independent prospective observational studies performed in Glasgow, United Kingdom.^{17, 18} Process for the validation was equivalent to that employed in the derivation studies. We included those stroke patients with relevant baseline and 90 day mortality data. In one dataset, initial stroke severity was assessed using Scandinavian Stroke Scale (SSS) rather than NIHSS. We transformed SSS into NIHSS using a validated process.¹⁹

Statistical Methods

We used standard descriptive statistics for the cohort. We described mean (standard deviation, SD) or median (IQR) for continuous variables and count (percentage) for categorical variables. In order to assign an integer score for baseline NIHSS into the modified-SOAR score, we categorized the NIHSS scores into four categories; 1-4, 5-10, 11-20 and ≥ 21 . The designated integer values for baseline NIHSS was obtained by rounding the log-ORs to the nearest integer.¹⁵ To keep scoring aligned with original SOAR scores, we further collapsed NIHSS categories 11-20 and greater than ($>$)20 into a single category of >11 . (Supplementary Table I)

We calculated odd ratios (ORs) and 95% confidence intervals (95%CI) for early (90 day) mortality using univariable and multivariable logistic regression models. Associated p-values were calculated using the Cochran-Mantel-Haenszel test.

Outcome of interest is early mortality. We compared discrimination of SOAR and mSOAR using c-statistics (Area under the Receiver Operating Curve, [AUROC]) for each scale. We calculated the Net Reclassification Index (NRI) and the Integrated Discrimination Improvement (IDI) as a result of adding NIHSS to the original SOAR score. The NRI measures the correctness of reclassification of subjects based on their predicted probabilities of events using the new model with the option of imposing meaningful risk categories.^{20, 21} The IDI measures the new model's improvement in average sensitivity without sacrificing average specificity.^{20, 21} NRI and IDI are methods to measure the increase (or decrease) in predicted probabilities for those who have (or have not) an event of interest.^{20, 21} We assessed calibration using Hosmer-Lemeshow goodness-of-fit tests. We also performed the sensitivity analysis in the validation cohort for outcome of mortality within 10 days.

Analyses were undertaken using SAS version 9.3 (SAS Institute, Inc, Cary NC) and Stata version 11.0 (Stata Corporation, College Station, TX, USA).

RESULTS

Derivation cohort: Of the 8756 total acute stroke patients in the ASHCN registry (2008-2011), we used data for 1002 (11%) patients, who had complete baseline data for individual items of the SOAR/ m-SOAR scores. The main missing variable was NIHSS as this was not routinely assessed. The characteristics of those with NIHSS observed and those with missing NIHSS data within the ASHCN registry during the study period are shown in Supplementary Table II. The cohort with complete baseline data to form the SOAR/ mSOAR scores had median age of 78 (IQR: 69-85) years; 465 (46%) were female; median baseline NIHSS of 6 (3-13). (Table 1) One hundred and five (10.5%) patients died as in-patient. (Table 2)

The median SOAR score was 2 (IQR: 1-3). The proportions of early mortality post-stroke varied according to the original SOAR scores (Supplementary Table III).

The median mSOAR score for the cohort was 3 (IQR: 2-5). The proportions of early death post-stroke varied according to individual modified-SOAR scores from 1% early mortality for mSOAR of 0-1 to 49% early mortality for mSOAR of 7. (Table 2) The observed risks for increasing value of the mSOAR score in Table 2 were very similar to those predicted from the logistic regression model. The predicted value for each mSOAR scores, 0 to 7, were 1.0%, 1.5%, 6.5%, 9.2%, 19.5%, 26.2% and 49.2%, respectively. These are very close to the observed risks and hence we have based our 'predicted values' on the observed risks of the derivation cohort.

Prognostic accuracy metrics (sensitivity, specificity, positive and negative predictive values) for predicting early mortality varied according to mSOAR with a "trade-off" between sensitivity and specificity particularly evident at extremes of scoring. (Table 3)

The mSOAR score that appeared to show optimal prognostic accuracy was at cut-off score of 3 (i.e. mSOAR \geq 4).

The discrimination of the original SOAR and mSOAR scores, using AUROC, were 0.79 (95%CI: 0.75-0.84) and 0.83 (95%CI: 0.79- 0.86), respectively, with a significant difference in favor of mSOAR ($p=0.001$). (Supplementary Figure I, Supplementary Figure II, and Figure 1) Calibration suggested that the mSOAR model gave reasonable fit to the data was good ($p=0.67$ for the Hosmer-Lemeshow test).

Validation cohort: The two studies that comprised the external validation cohort included 1091 patients of whom 1012 (93%) had full data to allow SOAR/ mSOAR scoring and outcomes analyses. The remaining patients were excluded due to missing data. The median age of the validation cohort was 71 (IQR: 61-79) years; with 497 (49%) were female and median baseline NIHSS was 5 (IQR: 2-11). (Table 1) One hundred and twenty one (12.0%) patients died within 90 days post-stroke. (Table 2)

The median original SOAR score for the validation cohort was 1 (IQR:1-2). In contrast, the median mSOAR score for similar cohort was 2 (IQR:1-4). The proportions of early death post-stroke varied according to mSOAR scores from 3% for mSOAR score of 0-1 to 42% for mSOAR of 7. (Table 2) The AUROC of the modified-SOAR score performed using the validation cohort was 0.84 (95%CI: 0.82-0.88) for outcome of early mortality. Calibration suggested that the mSOAR model gave a reasonable fit to the data ($p=0.70$ for the Hosmer-Lemeshow test). (Figure 2)

For the derivation cohort the NRI was 66.7% ($n=547$ recoded to a lower risk category and $n=76$ recoded to a higher risk category). For the validation cohort the NRI was 62.5% ($n=662$ recoded to lower risk and $n=78$ recoded to higher risk). (Supplementary Table IV

and V) The IDI in sensitivity across all possible cut-offs is 4% for both of the original SOAR and mSOAR scores.

Sensitivity analysis: Results of sensitivity analysis performed on the validation cohort for outcome of mortality within 10 days post-stroke are available in the Supplementary Table VI and Supplementary Figure III. Briefly, 98 (81%) patients died within 10 days post-stroke. The proportion of patients with 10 day mortality post-stroke according to mSOAR score mirrored the proportion of patients with 90 day mortality post-stroke, apart from patients who had the highest mSOAR score of 7. The AUROC of the mSOAR score for outcome of death within 10 days post-stroke was comparable with the AUROC of death within 90 days, 0.81 (95%CI: 0.77-0.85) and 0.83 (95%CI: 0.79- 0.86), respectively. (Supplementary Figure III).

DISCUSSION

Our findings suggest that the addition of an initial stroke severity scale (NIHSS) may significantly improve prognostic accuracy of the SOAR score for predicting early mortality post stroke. We believe our modified “mSOAR” score offers prognostic utility while remaining relatively easy to score. A criticism of previous studies that have suggested favorable properties of prognostic tools has been lack of replication. We performed validation analyses using an independent and geographically distinct population. Prognostic utility of mSOAR was confirmed in this cohort.

Although several stroke prognosis scales are described few have been adopted for widespread clinical use. An example of a prognostic tool that has translated into practice is the ABCD₂ risk score for transient ischemic attack.²² We believe mSOAR shares several features with ABCD₂ that should make it attractive to clinical teams. The input covariates of mSOAR are easily available, in fact most of the features needed to score mSOAR are recorded as standard in national stroke audits. We recognize that pre-morbid mRS is an imperfect measure but it remains the most common method of describing pre-stroke functioning.²³ Further we and others have previously shown that pre-stroke mRS is an independent predictor of stroke outcomes such as mortality and length of stay.^{24, 25} Creating a total mSOAR score is also straightforward with only five variables requiring scoring and no need for external software or complicated arithmetic. Derivation and validation of mSOAR was based on a heterogenous population and so the score should be applicable to all stroke syndromes.

Our study had a specific hypothesis around adding a marker of initial stroke severity to an existing prognostic tool. We recognised that stroke impairment measures such as NIHSS have prognostic value as a standalone assessment and so intuitively adding these data to SOAR should improve properties. Our approach could be applied to any of the other stand

alone or multivariate prognostic tools available in acute stroke. Indeed, future prognostic research in stroke requires further examination of which are the best predictors of various relevant outcomes including mortality and functional outcome both as standalone and as part of multivariable predictive tools. Perhaps, inclusion of other covariates especially more sophisticated or clinically relevant variables would improve the prognostic value. For example, the addition of neuroimaging finding to the ABCD₂ score²² (which resulted to ABCD_{3-I} score²⁶) improves the risk stratification after transient ischemic attack in secondary care settings.²⁶ Another example is the widely used and well-validated ASTRAL score, which includes time delay from stroke onset to admission, specific clinical signs at presentation and baseline glucose level.^{8, 27} It would also be informative to compare clinical utility of mSOAR against intuition of an experienced clinician. Future prognostic research perhaps should focus on utilising large composite datasets with comprehensive baseline data which would allow for such an analysis and help describe an optimal predictive covariate sets for relevant outcomes.

We describe an optimal performing cut point for our scale, this is the point of most equitable trade-off between false positives and false negatives. In practice the mSOAR score that has greatest utility will vary according to the purpose for which the score is used. For example, if clinicians wish to use the prognostic information to inform discussions around ceilings of care, they may prefer a cut point on the scale that minimises false positives.

A difficulty with mSOAR and indeed all stroke prognostic scales is *how* the clinician uses the tool. If decisions on pursuing or withholding treatment are to be based on a risk estimate then that estimate needs to be robust. Although mSOAR has favorable properties, that are comparable or better than many other prognostic tools, it is probably still not suitable as the sole basis for therapeutic decisions. Even at the optimal

performing cut point, mSOAR will suggest early mortality for a substantial proportion who go on to survive past ninety days and equally will suggest survival for a proportion who have early mortality. Nonetheless patients and families want early prognostic information and clinicians have to make therapeutic decisions based on likely prognosis each day. We believe mSOAR offers some structure and evidence base to inform prognostic assessment.

We agree the Net Reclassification Index (NRI) appears high. The NRI works best for dichotomous data.^{20, 21} Majority of the re-classifications in our data were within the 'low risk' categories hence the practical importance of these re-classifications will be limited. Thus, we believe that the NRI should be interpreted with caution and prefer the ROC as a better measure of the difference between the risk scores.

Strengths of our analysis include the large sample size, large number of “outcomes” and “real world” populations included. We believe our results will have greater external validity than prognostic scores derived and validated exclusively using selected clinical trial participants. Furthermore, for the first time we found SOAR and mSOAR are useful up to 90days post stroke mortality prediction. Despite the observable differences between the derivation and validation cohorts in terms of age and pre-stroke mRS, and the follow-up time points (in-hospital vs. within 90 days) the mSOAR score performed very similarly, and consistently which may indicate its generalizability.

A limitation of our derivation dataset was substantial missing NIHSS data. Our analysis comparing those with and without NIHSS suggests that missing NIHSS data were more likely to be associated with markers of poor outcome (age, pre-stroke mRS) and higher in-hospital mortality, approximately doubled the mortality risk. The data we used for our derivation work was from a clinical registry. At the time of data collection NIHSS assessment and recording in the registry was not mandatory. We acknowledge that those

with NIHSS recorded may be systematically different from those without, however the derivation cohort still has a spread of NIHSS and outcomes that are in keeping with data from other registries and so seem to have external validity. The effect of missing NIHSS could potentially bias the prognostic properties of mSOAR, but we are reassured that in our validation cohort (with good data capture for NIHSS) properties of mSOAR were similar to the derivation data. We also hope that the effect of any misreporting of key variables will be modest given our relatively large and similar size datasets for derivation and validation; and the internal and external quality control employed within such national registries. The final cohorts are all old and changes in stroke care may have impacted on early mortality and hence the properties of the tool. Of note, the derivation data was based on in-hospital mortality and we were unable to ascertain their vital status at 90-days. Nevertheless examination of ASCNES data (drawn from the same ASHCN database) with one year follow up data demonstrated that 81% of within 90 days were in-hospital deaths.

In conclusion, our results demonstrate the reliability of modified-SOAR score to predict early death in an acute stroke cohort. Adding NIHSS data to the original SOAR score, to create modified-SOAR score, improved the prognostic utility in both derivation and validation datasets. Modified-SOAR may potentially help clinicians better predict early stroke mortality.

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Author Contributions:

Dr Myint supervised the project. Drs Abdul-Rahim, Alder and Clark conducted the analyses. Drs Abdul-Rahim and Quinn drafted the initial manuscript. Drs Abdul-Rahim, Quinn, Clark and Myint involved in reviewing and reporting of the work. All authors provided critical revision of the manuscript for important intellectual content and approved the final version.

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TABLES

Table 1: Baseline characteristics of the derivation and validation cohorts, data are presented as per SOAR and mSOAR scoring.

| | Derivation (N=1002), n(%) | Validation (N=1012), n(%) |
|----------------------------|------------------------------|------------------------------|
| Age, median (IQR) | | |
| ≤65 | 191(19.1) | 355(35.1) |
| 66-85 | 595(59.4) | 563(55.6) |
| >85 | 216(21.6) | 94(9.3) |
| Sex | | |
| Female | 465(46.4) | 497(49.1) |
| Stroke subtype | | |
| Infarction (ischemic) | 929(92.7) | 924(91.3) |
| OSCP classification | | |
| LACS/PACS | 661(66.0) | 663(66.2) |
| POCS | 134(13.4) | 93(9.3) |
| TACS | 207(20.7) | 246(24.5) |
| Pre-stroke mRS | | |
| mRS 0-1 | 850(84.8) | 877(86.7) |
| mRS 2-3 | 139(13.9) | 130(12.9) |
| mRS 4-5 | 13(1.3) | 5(0.4) |
| Baseline NIHSS, | | |
| NIHSS 0-4 | 363(36.2) | 379(37.5) |
| NIHSS 5-10 | 326(32.5) | 303(29.9) |
| NIHSS ≥11 | 313(31.2) | 330(32.6) |

OCSP indicates Oxford Stroke Classification Project; LACS: lacunar Stroke; PACS: partial anterior circulation stroke; POCS: posterior circulation stroke; TACS: total anterior circulation stroke, NIHSS: National Institutes of Health Stroke Scale.

Table 2: Comparison of derivation and validation results of modified-SOAR score.

| Modified-SOAR score level | Derivation cohort | | Validation cohort | |
|------------------------------|-------------------|---------------------------------------|-------------------|---------------------------------------|
| | Patient, n | Patient with early mortality, n(%) | Patient, n | Patient with early mortality, n(%) |
| 0 or 1 | 205 | 2(1.0) | 363 | 7(1.9) |
| 2 | 207 | 3(1.5) | 211 | 6(2.8) |
| 3 | 200 | 13(6.5) | 153 | 16(10.5) |
| 4 | 130 | 12(9.2) | 103 | 18(17.5) |
| 5 | 113 | 22(19.5) | 103 | 32(31.1) |
| 6 | 84 | 22(26.2) | 67 | 37(55.2) |
| 7 | 63 | 31(49.2) | 12 | 5(41.7) |

Table 3: Predictive value of early mortality (death within 90 days) by modified-SOAR score using various cut-off points.

| Cut point | n | Early mortality, n (%) | Sensitivity,% | Specificity,% | PPV,% | NPV,% |
|-----------|-----|------------------------|------------------|------------------|------------------|------------------|
| ≥2 | 797 | 103 (12.9) | 98.1 (93.3-99.8) | 22.6 (19.9-25.5) | 12.9 (10.7,15.5) | 99.0 (96.5,99.9) |
| ≥3 | 590 | 100 (16.9) | 95.2 (89.2-98.4) | 45.4 (42.1-48.7) | 16.9 (14.0-20.2) | 98.8 (97.2-99.6) |
| ≥4 | 390 | 87 (22.3) | 82.9 (74.3-89.5) | 66.2 (63.0-69.3) | 22.3 (18.3-26.8) | 97.1 (95.4-98.2) |
| ≥5 | 260 | 75 (28.8) | 71.4 (61.8-79.8) | 79.4 (76.6-82.0) | 28.8 (23.4-34.8) | 96.0 (94.3-97.3) |
| ≥6 | 147 | 53 (36.1) | 50.5 (40.5-60.4) | 89.5 (87.3-91.4) | 36.1 (28.3-44.4) | 93.9 (92.1-95.4) |
| ≥7 | 63 | 31 (49.2) | 29.5 (21.0-39.2) | 96.4 (95.0-97.5) | 49.2 (36.4-62.1) | 92.1 (90.2-93.8) |

The parameters presented are for that score cut-off point and above with 95% confidence interval. PPV indicates positive predictive value;

NPV: negative predictive value.

FIGURES and FIGURE LEGENDS

Figure 1: Area under the receiving operator curve (AUROC) of the modified-SOAR score for early mortality in the derivation cohort.

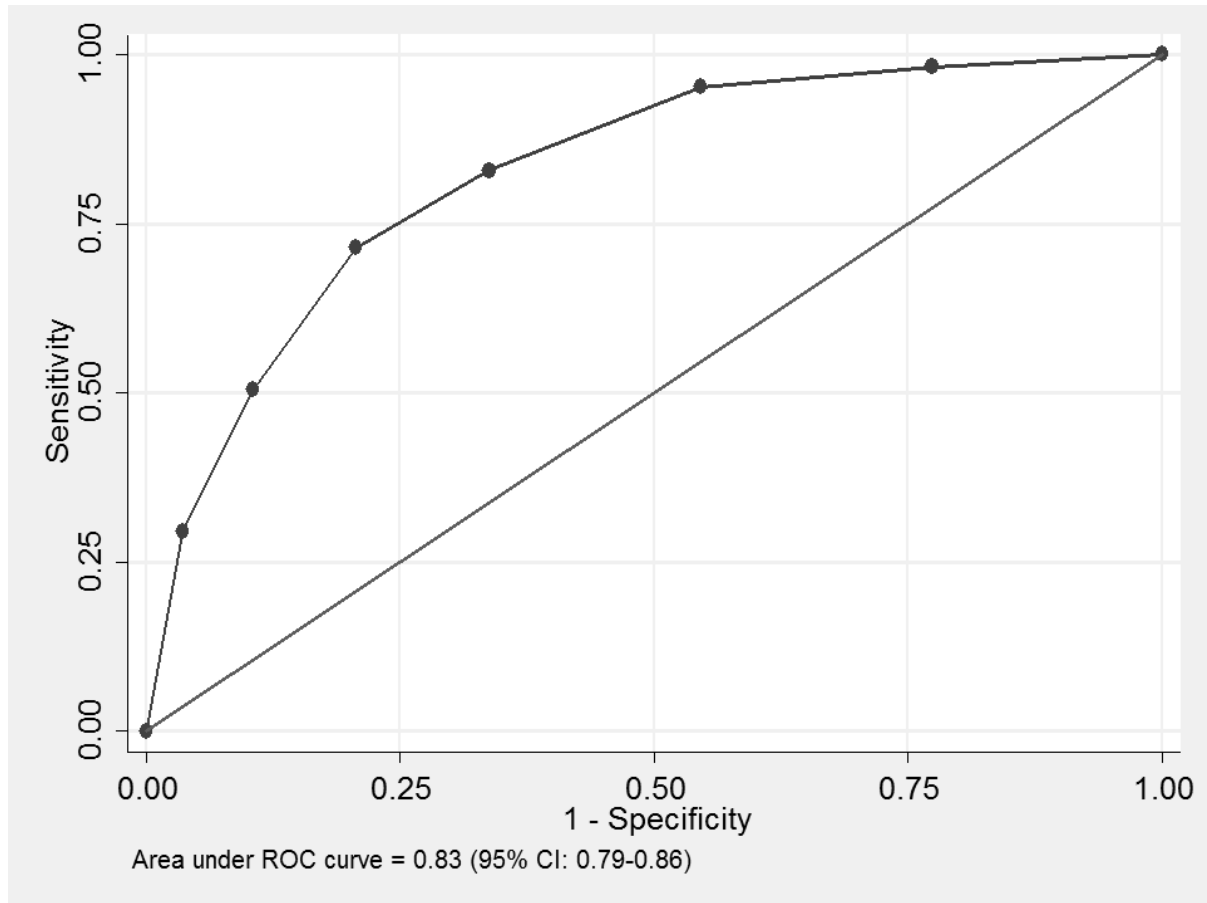


Figure 2: Area under the receiving operator curve (AUROC) of the modified-SOAR score for early mortality in the validation cohort.

