1. TRIPOD Checklist.
2. Criticality Index
3. Variables
4. Imputation
5. Model Derivation
6. TRIPOD Guidelines Checklist.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Section/Topic** | **Item** |  | **Checklist Item** | **Page** |
| **Title and abstract** |
| **Title** | **1** | **D;V** | **Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.** | **Done** |
| **Abstract** | **2** | **D;V** | **Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.** | **Done** |
| **Introduction** |
| **Background and objectives** | **3a** | **D;V** | **Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.** | **Intro paragraphs 1-3; Methods>Machine Learning> para 3; Discussion para 1-6; Conclusion.** |
| **3b** | **D;V** | **Specify the objectives, including whether the study describes the development or validation of the model or both.** | **Intro Para 3.**  |
| **Methods** |
| **Source of data** | **4a** | **D;V** | **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.** | **Methods> Sample** |
| **4b** | **D;V** | **Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.**  | **Methods>Sample** |
| **Participants** | **5a** | **D;V** | **Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.** | **Methods>Independent Variables and Methods>Machine Learning** |
| **5b** | **D;V** | **Describe eligibility criteria for participants.**  | **Methods>Sample** |
| **5c** | **D;V** | **Give details of treatments received, if relevant.**  | **NA** |
| **Outcome** | **6a** | **D;V** | **Clearly define the outcome that is predicted by the prediction model, including how and when assessed.**  | **Methods>Machine Learning>Para 2.** |
| **6b** | **D;V** | **Report any actions to blind assessment of the outcome to be predicted.**  | **Methods>Machine Leaning>para 1.** |
| **Predictors** | **7a** | **D;V** | **Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.** | **Methods>Variables** |
| **7b** | **D;V** | **Report any actions to blind assessment of predictors for the outcome and other predictors.**  | **Methods>Machine Learning>para 1** |
| **Sample size** | **8** | **D;V** | **Explain how the study size was arrived at.** | **Methods>Sample>Para 2** |
| **Missing data** | **9** | **D;V** | **Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.**  | **Methods>Independent Variables>para 1.** |
| **Statistical analysis methods** | **10a** | **D** | **Describe how predictors were handled in the analyses.**  | **Methods>Machine Learning** |
| **10b** | **D** | **Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.** | **Methods>Machine Learning and Supplemental Digital Content 1.** |
| **10c** | **V** | **For validation, describe how the predictions were calculated.**  | **Methods>Machine Learning** |
| **10d** | **D;V** | **Specify all measures used to assess model performance and, if relevant, to compare multiple models.**  | **Methods** |
| **10e** | **V** | **Describe any model updating (e.g., recalibration) arising from the validation, if done.** | **Methods>Machine Learning> Para 1.** |
| **Risk groups** | **11** | **D;V** | **Provide details on how risk groups were created, if done.**  | **Methods>Machine Learning>para 2.** |
| **Development vs. validation** | **12** | **V** | **For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.**  | **Methods> Machine Learning >Para 1** |
| **Results** |
| **Participants** | **13a** | **D;V** | **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.**  | **Results>Para 1.** |
| **13b** | **D;V** | **Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.**  | **Results >Para 1**  |
| **13c** | **V** | **For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).**  | **ND. Randomized samples.** |
| **Model development**  | **14a** | **D** | **Specify the number of participants and outcome events in each analysis.**  | **Yes, throughout Results** |
| **14b** | **D** | **If done, report the unadjusted association between each candidate predictor and outcome.** | **ND, not relevant for this modelling** |
| **Model specification** | **15a** | **D** | **Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).** | **Machine leaning not practical.**  |
| **15b** | **D** | **Explain how to the use the prediction model.** | **Discussion Para 1,**  |
| **Model performance** | **16** | **D;V** | **Report performance measures (with CIs) for the prediction model.** | **Done,** |
| **Model-updating** | **17** | **V** | **If done, report the results from any model updating (i.e., model specification, model performance).** | **NA** |
| **Discussion** |
| **Limitations** | **18** | **D;V** | **Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).**  | **Discussion>last para** |
| **Interpretation** | **19a** | **V** | **For validation, discuss the results with reference to performance in the development data, and any other validation data.**  | **Test sample reporter and discussed Disc para 1** |
| **19b** | **D;V** | **Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.**  | **Discussion** |
| **Implications** | **20** | **D;V** | **Discuss the potential clinical use of the model and implications for future research.**  | **Discussion** |
| **Other information** |
| **Supplementary information** | **21** | **D;V** | **Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.**  | **Code offered>author page.** |
| **Funding** | **22** | **D;V** | **Give the source of funding and the role of the funders for the present study.**  | **Author page** |

**2A. Criticality Index Independent Variables**. Modified from: Rivera EAT, Patel AK, Chamberlain JM, Workman TE, Heneghan JA, Redd D, Morizono H, Kim D, Bost JE, Pollack MM. Criticality: A New Concept of Severity of Illness for Hospitalized Children. Pediatr Crit Care Med. 2021 Jan 1;22(1):e33-e43. doi: 10.1097/PCC.0000000000002560. PMID: 32932406; PMCID: PMC7790867.

|  |  |  |  |
| --- | --- | --- | --- |
| **Lab Variables1,3,4** | **Vital Signs1,3,4** | **Medications2,3** | **Other** |
| Albumin | Bilirubin Indirect | Hemoglobin | Platelets | BP-systolic | 1113 individual medications | AgeSex |
| ALT | Bilirubin Total | Hematocrit | Potassium | BP- diastolic | 143 medication categories (6) | Mechanical Ventialiton |
| Arterial Lactate | BUN | INR | Protime | Heart Rate |  |  |
| PO2 (arterial) | Calcium | Glucose | Sodium | Respiratory Rate |  |  |
| AST | Calcium Ionized | PTT | Total Protein | Temperature |  |  |
| Base Excess | Chloride | PCO2 (5) | Venous Lactate | Coma Score |  |  |
| Bicarbonate | Creatinine | pH (5) | WBC |   |  |  |
| Bilirubin Direct | Fibrinogen |   |   |   |  |  |
| 1. Summarized for modeling with the following statistics for each variable: the count, sample mean, sample standard deviation (0 if the count was <2), maximum, and minimum.
2. Summarized for modeling with the following statistics: the 6-hour sum per medication category of the number of medications given each hour; 2) the count of the previous time periods per medication category that the patient received one or more medications; 3) the proportion of the previous time periods per medication category that the patient received one or more medications.
3. Therapeutic intensity is reflected in the number of vital sign and laboratory measurements and medications.
4. If during the first six-hour time period there were missing values, these values were adjusted to the median of the first six hour time periods adjusted to the following age groups: <1week, 1week-<4weeks, 4weeks-<3months, 3months-<1year, 1year-<2years, 2years-<3years, 3years-<8years, 8years-<12years, 12years-<22years.
5. Arterial, venous, capillary.
6. Classified by Multum.
 |  |

**2B. Imputed Values for Laboratory and Vital Sign Data by Age.** Modified from supplemental digital content in: Rivera EAT, Patel AK, Chamberlain JM, Workman TE, Heneghan JA, Redd D, Morizono H, Kim D, Bost JE, Pollack MM. Criticality: A New Concept of Severity of Illness for Hospitalized Children. Pediatr Crit Care Med. 2021 Jan 1;22(1):e33-e43. doi: 10.1097/PCC.0000000000002560. PMID: 32932406; PMCID: PMC7790867.

The initial time period required values for all laboratory and vital sign data. We imputed the values from the medians by age groups of those patients who had these measurements in the first time period. Note, that the imputed data also included the measurement count for the test which was set to 0 to indicate an imputed value. The age groups were a composite of the age groups used for display of normal data by various sources.

**Laboratory Data. Values are medians.**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Age Groups** | **Albumin** | **ALT** | **Arterial PO2** | **AST** | **Base Excess** |
|  |  |  |  |  |  |
| [1hr,1wk) | 2.8 | 15 | 68 | 54 | -4 |
| [1wk,4wks) | 3.1 | 22 | 61.5 | 39 | -0.2 |
| [4wks,3mnths) | 3.3 | 25 | 61 | 39 | 0.5 |
| [3mnths,1yr) | 3.6 | 26 | 77.5 | 43 | -0.9 |
| [1yr,2yrs) | 3.8 | 23 | 91 | 43 | -3.9 |
| [2yrs,3yrs) | 3.8 | 22 | 119 | 41 | -2 |
| [3yrs,8yrs) | 3.8 | 19 | 113 | 37 | -2 |
| [8yrs,12yrs) | 3.9 | 19 | 129 | 30 | -2.75 |
| [12yrs,22yrs) | 3.8 | 20 | 139 | 25 | -3 |
|  |  |  |  |  |  |
|  |  |  |  |  |  |
|  | **Direct bilirubin** | **Indirect bilirubin** | **Total bilirubin** | **BUN** | **Calcium** |
| [1hr,1wk) | 0.4 | 6 | 7.25 | 9 | 9 |
| [1wk,4wks) | 0.4 | 4.6 \*\* | 2.25 | 9 | 9.9 |
| [4wks,3mnths) | 0.3 | 0.9 | 0.5 | 9 | 9.8 |
| [3mnths,1yr) | 0.1 | 0.4 | 0.3 | 9 | 9.8 |
| [1yr,2yrs) | 0.1 | 0.3 | 0.3 | 11 | 9.6 |
| [2yrs,3yrs) | 0.1 | 0.4 | 0.3 | 11 | 9.5 |
| [3yrs,8yrs) | 0.1 | 0.4 | 0.4 | 11 | 9.4 |
| [8yrs,12yrs) | 0.2 | 0.5 | 0.4 | 11 | 9.3 |
| [12yrs,22yrs) | 0.2 | 0.5 | 0.4 | 11 | 9 |
|  |  |  |  |  |  |
|  | **Ionized Calcium** | **Chloride** | **Creatinine** | **Fibrinogen** | **Glucose** |
| [1hr,1wk) | 1.2 | 106 | 0.64 | 201.5 | 72 |
| [1wk,4wks) | 1.2974 | 104 | 0.405 | 272.85 | 87.5 |
| [4wks,3mnths) | 1.32235 | 105 | 0.33 | 265 | 94.5 |
| [3mnths,1yr) | 1.26 | 104 | 0.32 | 307.5 | 101 |
| [1yr,2yrs) | 1.2 | 104 | 0.31 | 275 | 97 |
| [2yrs,3yrs) | 1.235 | 104 | 0.33 | 262 | 96 |
| [3yrs,8yrs) | 1.1976 | 104 | 0.4 | 324.5 | 100 |
| [8yrs,12yrs) | 1.17265 | 103 | 0.5 | 333.5 | 104 |
| [12yrs,22yrs) | 1.14 | 104 | 0.7 | 341.5 | 105 |
|  |  |  |  |  |  |
|  | **HCO3** | **Hematocrit** | **Hemoglobin** | **INR** | **Arterial Lactate** |
| [1hr,1wk) | 23 | 47.5 | 16.2 | 1.29 | 1.43 |
| [1wk,4wks) | 24 | 39.55 | 13.6 | 1.31 | 1.19 |
| [4wks,3mnths) | 24.8 | 31.05 | 10.6 | 1.08 | 1.81 |
| [3mnths,1yr) | 22.45 | 33.8 | 11.4 | 1.26 | 1 |
| [1yr,2yrs) | 21 | 34.3 | 11.5 | 1.205 | 1.22 |
| [2yrs,3yrs) | 22 | 34.1 | 11.6 | 1.09 | 1 |
| [3yrs,8yrs) | 23 | 34.5 | 11.8 | 1.245 | 1.7 |
| [8yrs,12yrs) | 24 | 36.3 | 12.4 | 1.14 | 1.85 |
| [12yrs,22yrs) | 24 | 37.3 | 12.6 | 1.2 | 2.195 |
|  |  |  |  |  |  |
|  | **Venous Lactate** | **PTT** | **PCO2** | **pH** | **Platelet Count** |
| [1hr,1wk) | 2.35 | 42.4 | 43.1 | 7.31 | 227 |
| [1wk,4wks) | 3.15 | 39 | 44.3 | 7.35 | 338 |
| [4wks,3mnths) | 3.77 | 35.15 | 50 | 7.34 | 378 |
| [3mnths,1yr) | 2.2 | 32 | 45 | 7.35 | 339 |
| [1yr,2yrs) | 1.8 | 29 | 39.6 | 7.35 | 313 |
| [2yrs,3yrs) | 1.3 | 29 | 39.05 | 7.34 | 290 |
| [3yrs,8yrs) | 2 | 29 | 39 | 7.35 | 274 |
| [8yrs,12yrs) | 2.3 | 29 | 37 | 7.32 | 266 |
| [12yrs,22yrs) | 2.2 | 28.4 | 36 | 7.333 | 239 |
|  |  |  |  |  |  |
|  | **Potassium** | **Protime** | **Sodium** | **Total Protein** | **White Blood Cell Count** |
| [1hr,1wk) | 4.6 | 15.1 | 139 | 5.2 | 13.9 |
| [1wk,4wks) | 5 | 14.4 | 138 | 5.5 | 11.3 |
| [4wks,3mnths) | 5 | 13.8 | 138 | 5.5 | 10.85 |
| [3mnths,1yr) | 4.6 | 14 | 138 | 6.1 | 11.305 |
| [1yr,2yrs) | 4.3 | 12.4 | 138 | 6.8 | 12 |
| [2yrs,3yrs) | 4.2 | 12.35 | 138 | 6.8 | 10.4 |
| [3yrs,8yrs) | 4 | 12.4 | 138 | 6.9 | 10.2 |
| [8yrs,12yrs) | 4 | 12.4 | 138 | 7.1 | 9.705 |
| [12yrs,22yrs) | 3.9 | 13 | 139 | 7 | 10.5 |

**Vital Signs. Values are medians.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Age Group** | **Systolic BP** | **Diastolic BP** | **Coma Score** | **Heart Rate** | **Respiratory Rate** | **Temperature (Centigrade)** |
| [1hr,1wk) | 63 | 35 | 14 | 150 | 48 | 36.8 |
| [1wk,4wks) | 76 | 45 | 14 | 159 | 41 | 36.9 |
| [4wks,3mnths) | 87 | 49 | 14 | 158 | 40 | 36.9 |
| [3mnths,1yr) | 99 | 57 | 14 | 148 | 38 | 36.8 |
| [1yr,2yrs) | 107 | 64 | 15 | 141 | 30 | 37.1 |
| [2yrs,3yrs) | 108 | 64 | 15 | 133 | 27 | 36.9 |
| [3yrs,8yrs) | 106 | 64 | 15 | 120 | 24 | 37.0 |
| [8yrs,12yrs) | 112 | 67 | 15 | 106 | 21 | 36.9 |
| [12yrs,22yrs) | 120 | 70 | 15 | 96 | 19 | 36.8 |

Sources for Age-Normals

<https://testdirectory.questdiagnostics.com/test/test-detail/6631/?cc=MASTER>.

<https://www.accp.com/docs/sap/Lab_Values_Table_PedSAP.pdf>.

[https://www.unboundmedicine.com/harrietlane/view/Harriet\_Lane\_Handbook/309269/all/TABLE\_27\_1:\_Reference\_Values](https://www.unboundmedicine.com/harrietlane/view/Harriet_Lane_Handbook/309269/all/TABLE_27_1%3A_Reference_Values).

<https://pdfs.semanticscholar.org/7106/09b4b2d315e448b4267a49420e1080da25eb.pdf>.

[file:///Q:/PediatricBloodGasesCriticalCarePanelTransportandECMOAgeRelatedReferenceandcv103117%20(2).pdf](file:///Q%3A%5CPediatricBloodGasesCriticalCarePanelTransportandECMOAgeRelatedReferenceandcv103117%20%282%29.pdf).

**2C. Machine Learning Model: Expanded Description.** Modified from: Trujillo Rivera EA, Chamberlain JM, Patel AK, Zeng-Treitler Q, Bost JE, Heneghan JA, Morizono H, Pollack MM. Predicting Future Care Requirements Using Machine Learning for Pediatric Intensive and Routine Care Inpatients. Crit Care Explor. 2021 Aug 10;3(8):e0505. doi: 10.1097/CCE.0000000000000505. PMID: 34396143; PMCID: PMC8357255.

The Criticality Index is the risk that the patient will receive ICU care. The Criticality Index is computed using a neural network trained to maximize the Mathew Correlation Coefficient (MCC) in the classification task of ICU/no ICU time periods. The calibration of the neural network to risk of ICU care results the output of the model as the Criticality Index.

The neural network is sequential, and layers are fully connected. The model has seven hidden dense layers, an output layer with one node and logistic activation. Inputs for the models include variables of the present and immediate past time period. The resulting model architecture is the result of sequential architecture experimentation for the task of maximizing the Mathew Correlation Coefficient (MCC) on the resulting classification task with a threshold of 0.5. As a first step, only models with one hidden layer were considered. Sequential increase of the number of internal nodes in combination with dropout nodes proportions, and L2 norm regularization, directed the final number of nodes for the first hidden layer. We stopped increasing the number of nodes in the hidden layer when the sequence of MCCs on the validation set, as epochs continue, deviated considerably with respect to the training set, and seemed to have converged to a common value. When we concluded it was not possible to increase the MCC of both the training and validation set, the first hidden layer was frozen, and a second hidden layer was added. Construction of the final second layer architecture is similar to the process described, but with the first hidden layer architecture frozen. Consecutive hidden layers were added while the previous hidden layer architectures were frozen. We ceased adding hidden layers when it did not significantly improve the MCC of both the training and validation sets. Care was taken to not overfit by keeping the MCC of the training and validation sets at a difference of no larger than 0.05. The validation set, and the test set must have similar distributions as they are both random samples from a common set of patients. Therefore, it is expected that the MCC, and all other metrics are similar on the test set.

The resulting neural network was calibrated to the risk of ICU care need using a single polynomial b-splines of degree 3 on the training and validation sets. The splines inputs are the output of the neural network, and the outcome is binary (ICU vs no-ICU care) in the respective time periods. The consecutive use of the described neural network and then of fitted b-splines plate spline, is the calibrated (to risk of ICU) neural network. The output of the calibrated neural network is the criticality index of the time period computed using the most recent physiological and treatment information of the patient.

In the present manuscript we use the calibrated neural network as basis for predicting hospital mortality by recalibrating its output to risk of hospital mortality. Each time period from each patient has an associated Criticality Index, and an associated additional indicator variable of mechanical ventilation. These two variables were associated with the binary outcome of survival or death. For a fixed time after ICU admission, we fitted a thin plate spline using the time period from each encounter that contains the fixed time period after ICU admission. The thin plate spline was fitted with interaction and the marginal the two variables in an additive way [1,2] The smoothing parameters were computed using cross validation. A different thin plate spline was fitted for each time period after ICU admission.

Each model was independently calibrated to the future risk of hospital mortality.

1. Gu C. Smoothing Spline ANOVA Models. Springer Series in Statistics; 2002.
2. Gu C. Smoothing Spline ANOVA Models: R Package gss. *Journal of Statistical Software* 2014; 58(5):1-25. doi:10.18637/jss.v058.i05