# Supplementary Material

**Computer Aided Risk Score for Sepsis (CARS)**

The CARS equation is shown below:-

We accounted for baseline difference in sepsis risk in the external validation data by adding 0.32 to the CARS logit model using an iterative procedure described elsewhere1

1. Faisal M, Howes R, Steyerberg EW, Richardson D, Mohammed MA. Using routine blood test results to predict the risk of death for emergency medical admissions to hospital: an external model validation study. QJM [Internet]. 2017 Jan 1 [cited 2017 Oct 2];110(1):27–31. Available from: https://academic.oup.com/qjmed/article-lookup/doi/10.1093/qjmed/hcw110

**The National Early Warning Score (NEWS)**

The NEWS [https://www.rcplondon.ac.uk/projects/outputs/national-early-warning-score-news] is based on a scoring system in which a score is allocated to vital signs physiological measurements already undertaken when patients present to, or are being monitored in hospital. Six physiological parameters form the basis of the scoring system:

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Physiological Parameters** | **3** | **2** | **1** | **0** | **1** | **2** | **3** |
| **Respiration Rate** | ≤8 |  | 9 - 11 | **12 - 20** |  | 21 - 24 | ≥25 |
| **Oxygen Saturations** | ≤91 | 92 - 93 | 94 - 95 | **≥96** |  |  |  |
| **Any Supplemental Oxygen** |  | Yes |  | **No** |  |  |  |
| **Temperature** | ≤35.0 |  | 35.1 - 36.0 | **36.1 - 38.0** | 38.1 - 39.0 | ≥39.1 |  |
| **Systolic Blood Pressure** | ≤90 | 91 - 100 | 101 - 110 | **111 - 219** |  |  | ≥220 |
| **Heart Rate** | ≤40 |  | 41 - 50 | **51-90** | 91 - 110 | 111 - 130 | ≥131 |
| **Level of Consciousness** |  |  |  | **Alert** |  |  | Voice, Pain, or Unconscious |

A score is allocated to each as they are measured, the magnitude of the score reflecting how extreme the parameter varies from the norm. This score is then aggregated, and uplifted for people requiring oxygen. Note that diastolic blood pressure is not part of the NEWS scoring system, but is included in CARS because it is also routinely collected.

Figure S1 Boxplots (without outliers) for continuous covariates with and without sepsis (includes sepsis without organ failure, and severe sepsis with organ failure or septic shock) in the development dataset.

## Figure S2 Boxplots (without outliers) for continuous covariates with and without sepsis (includes sepsis without organ failure, and severe sepsis with organ failure or septic shock) in the external validation dataset.



Figure S3 Scatter plots showing the observed risk of sepsis (includes sepsis without organ failure, and severe sepsis with organ failure or septic shock) for continuous covariates in the development dataset.

NB: y-axis range changes in each plot.



Figure S4 Scatter plots showing the observed risk of sepsis (includes sepsis without organ failure, and severe sepsis with organ failure or septic shock) for continuous covariates in the external validation dataset.

NB: y-axis range changes in each plot.

**Figure S5: Discrimination of predicted risks of CARS in the development dataset (top row)** (A) All sepsis (B) sepsis without organ failure (C) Severe sepsis (with organ failure or septic shock) **and likewise for external validation dataset (bottom row)**



Figure S6 Internal and external validation calibration plot for CARS in the development dataset and validation dataset.

Left: Internal validation; Right: External validation

**Figure S7: Sensitivity analysis CARS in each category of sepsis at various thresholds (0.1, 0.2, 0.3) in the development dataset and external validation dataset.**

Black solid line is for sensitivity and black dashed line is for positive predictive value (PPV). Grey solid line is specificity and grey dashed vertical lines are at thresholds (0.01, 0.03, and 0.05).



Figure S8 Receiver operating characteristic curve for CARS-S for sepsis in (median) imputed records in the development dataset and the external validation dataset.

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| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Characteristic** | **Development Dataset (YH)** | | | | **Validation Dataset (NH)** | | | |
| **All**  **N=26247** | **No Sepsis**  **N=21386** | **Sepsis**  **N=3474** | **Severe Sepsis**  **N=1387** | **All**  **N=30996** | **No Sepsis**  **N=23223** | **Sepsis**  **N=****4909** | **Severe Sepsis**  **N=2864** |
| Died in hospital (%) | 1703 (6.5) | 999 (4.7) | 302 (8.7) | 402 (29.0) | 1766 (5.7) | 867 (3.7) | 287 (5.9) | 612 (21.4) |
| Mean Age [years] (SD) | 68.3 (19.2) | 66.7 (19.8) | 74.5 (14.7) | 77.4 (12.9) | 67.0 (19.3) | 64.2 (20.1) | 73.6 (15) | 77.9 (11.9) |
| Male (%) | 12491 (47.6) | 10217 (47.8) | 1596 (45.9) | 678 (48.9) | 15454 (49.9) | 11828 (50.9) | 2225 (45.3) | 1401 (48.9) |
| Mean NEWS (SD) | 2.6 (2.6) | 2.3 (2.4) | 3.8 (3) | 4.7 (3.4) | 2.2 (2.3) | 1.8 (2) | 3.1 (2.5) | 3.9 (3) |
| **Alertness** |  |  |  |  |  |  |  |  |
| Alert (%) | 25456 (97.0) | 20830 (97.4) | 3341 (96.2) | 1285 (92.7) | 30401 (98.1) | 22843 (98.4) | 4807 (97.9) | 2751 (96.1) |
| Pain (%) | 180 (0.7) | 130 (0.6) | 28 (0.8) | 22 (1.6) | 111 (0.3) | 78 (0.3) | 13 (0.3) | 20 (0.7) |
| Voice (%) | 463 (1.7) | 309 (1.5) | 85 (2.5) | 69 (5.0) | 398 (1.3) | 239 (1.0) | 77 (1.6) | 82 (2.9) |
| Unconscious (%) | 148 (0.6) | 117 (0.6) | 20 (0.6) | 11 (0.8) | 86 (0.3) | 63 (0.3) | 12 (0.3) | 11 (0.4) |
| **AKI Score** |  |  |  |  |  |  |  |  |
| 0 (%) | 23069 (87.9) | 19308 (90.3) | 2981 (85.8) | 780 (56.2) | 28389 (91.6) | 21736 (93.6) | 4672 (95.2) | 1981 (69.2) |
| 1 (%) | 1933 (7.4) | 1258 (5.9) | 350 (10.1) | 325 (23.4) | 1562 (5.0) | 933 (4.0) | 188 (3.8) | 441 (15.4) |
| 2 (%) | 560 (2.1) | 341 (1.6) | 66 (1.9) | 153 (11.0) | 558 (1.8) | 274 (1.2) | 28 (0.6) | 256 (8.9) |
| 3 (%) | 685 (2.6) | 479 (2.2) | 77 (2.2) | 129 (9.3) | 487 (1.6) | 280 (1.2) | 21 (0.4) | 186 (6.5) |
| Oxygen supplementation (%) | 3131 (11.9) | 1994 (9.3) | 726 (20.9) | 411 (29.6) | 6264 (20.2) | 3328 (14.3) | 1710 (34.8) | 1226 (42.8) |
| Mean Albumin [g/L] (SD) | 37.9 (5.8) | 38.5 (5.7) | 35.5 (5.4) | 34.1 (5.7) | 33.4 (6.1) | 34.4 (5.9) | 31 (5.7) | 29.1 (5.9) |
| Mean Creatinine [umol/L] (SD) | 103.2 (93.1) | 100.2 (91) | 100.2 (84.3) | 156.9 (124.5) | 105.9 (82.2) | 101.9 (79.1) | 93.8 (53.2) | 158.8 (120.3) |
| Mean Haemoglobin [g/l] (SD) | 124.7 (22.2) | 125.7 (22.2) | 120.6 (21.2) | 118.9 (22.8) | 127.2 (22.4) | 128.9 (22.5) | 123.9 (20.4) | 119.4 (22.1) |
| Mean Potassium [mmol/L] (SD) | 4.3 (0.6) | 4.3 (0.6) | 4.2 (0.6) | 4.4 (0.7) | 4.1 (0.6) | 4.1 (0.6) | 4 (0.6) | 4.3 (0.8) |
| Mean Sodium [mmol/L] (SD) | 136.6 (4.7) | 136.7 (4.5) | 135.8 (5.1) | 136.3 (6.2) | 136.9 (5.2) | 137.2 (4.9) | 135.9 (5.4) | 136.3 (6.8) |
| Mean White cell count [10^9 cells/L] (SD) | 10.4 (11.7) | 9.9 (11.9) | 12.1 (8.6) | 13.6 (13.9) | 10.0 (7.1) | 9.3 (5.6) | 11.7 (9.3) | 12.5 (11.4) |
| Mean Urea [mmol/L] (SD) | 8.2 (6.0) | 7.8 (5.7) | 8.2 (5) | 13.7 (9.3) | 7.9 (6.2) | 7.3 (5.5) | 7.3 (4.3) | 13.6 (9.9) |
| Mean Respiratory rate  [breaths per minute] (SD) | 18.8 (4.8) | 18.3 (4.4) | 20.6 (5.8) | 21.6 (6.7) | 18.1 (3.6) | 17.8 (3.3) | 19 (3.7) | 19.6 (4.8) |
| Mean Temperature [oC] (SD) | 36.3 (0.9) | 36.2 (0.8) | 36.7 (1) | 36.4 (1.1) | 36.5 (0.7) | 36.4 (0.6) | 36.7 (0.7) | 36.5 (0.8) |
| Mean Systolic pressure [mmHg] (SD) | 135.6 (27.5) | 136.4 (27.1) | 133.6 (28.2) | 128.5 (29.7) | 129.1 (23.0) | 130.5 (22.8) | 126.5 (22.2) | 121.9 (24.2) |
| Mean Diastolic pressure [mmHg] (SD) | 75.2 (15.6) | 75.8 (15.5) | 73 (15.7) | 70.4 (16.7) | 74.6 (14.9) | 75.8 (14.8) | 72.3 (14.5) | 69 (15.4) |
| Mean Pulse rate [beats per minute] (SD) | 86.6 (21.1) | 85.1 (20.7) | 92.9 (21.2) | 93.2 (23.8) | 81.6 (17.9) | 80.1 (17.6) | 86 (17.4) | 86.2 (18.9) |
| Mean % Oxygen saturation (SD) | 96.3 (3) | 96.5 (2.7) | 95.1 (3.5) | 94.8 (4.5) | 95.9 (3.1) | 96.2 (2.8) | 95.1 (3.1) | 94.5 (4.1) |

**Table S1 Characteristics of emergency medical admissions in the development dataset and external validation dataset**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **Complete cases** | | | | **Missing cases** | | | |
|  |  | **All** | **No Sepsis (%)** | **Sepsis (%)** | **Severe Sepsis (%)** | **All** | **No Sepsis (%)** | **Sepsis (%)** | **Severe Sepsis (%)** |
| **Development dataset** | **N**  **(%)** | 26247 | 21386  (81.47) | 3474  (13.24) | 1387  (5.28) | 10504 | 9395  (91.65) | 877   (8.35) | 232  (2.21) |
|  | **Died (%)** | 1703 (6.50) | 999  (4.67) | 302  (8.69) | 402  (28.98) | 434 (4.13) | 277  (2.95) | 80  (9.12) | 77  (33.19) |
| **External Validation dataset** | **N**  **(%)** | 30996 | 23223  (74.92) | 4909  (15.84) | 2864  (9.24) | 6104 | 5248  (92.32) | 469 (7.68) | 387  (6.34) |
|  | **Died (%)** | 1766 (5.70) | 867  (3.73) | 287  (5.85) | 612  (21.37) | 405 (6.63) | 225 (4.29) | 47  (10.02) | 133  (34.37) |

**Table S2: Characteristics of emergency admissions with complete and missing observations in the development dataset and external validation dataset**