**Aubert Supplemental Materials**

**Description of Laboratory Measurements**

Midregional pro-adrenomedullin (ADM) was measured by immunofluorescence on heparin-plasma samples kept frozen at –20°C, using commercially available kits (B.R.A.H.M.S. MR-proADM KRYPTOR, B.R.A.H.M.S. GmbH, Neuendorfstrasse 25, 16761 Hennigsdorf, Germany).1 Copeptin was measured by immunofluorescence on EDTA-plasma samples, kept frozen at –20°C, using commercially available kits (B.R.A.H.M.S. Copeptin us KRYPTOR, B.R.A.H.M.S. GmbH, Neuendorfstrasse 25, 16761 Hennigsdorf, Germany).1 Cortisol was measured on serum samples using a commercially available electrochemiluminescence immunoassay (ECLIA) (Roche Cobas e601 Cortisol, Roche Diagnostics GmbH, Sandhofer Strasse 116, 68305 Mannheim, Germany).2 Prolactin was measured on EDTA-plasma samples using a commercially available ECLIA (Roche Cobas e601 Prolactin II, Roche Diagnostics GmbH, Sandhofer Strasse 116, 68305 Mannheim, Germany).3

**References**

1. Thermo Scientific. Helping scientists meet the challenges they face in the lab or in the field every day. http://www.thermoscientific.com/en/home.html.

2. Roche Cobas E170/Elecsys Cortisol reagent cn, data sheet 2016-04, V 19.

3. Roche Cobas E170/Elecsys Prolactin II reagent cn, data sheet 2016-03, V 6.1.

**Supplemental Table 1A.** LACE Index

|  |  |  |
| --- | --- | --- |
|  | **Attribute** | **Points** |
| L | **Length of stay, d**12 34-67-13≥14 | 123457 |
| A | **Acute (emergent) admission**  | 1 |
| C | **Comorbidity (Charlson Comorbidity Index)** 0123≥4 | 01235 |
| E | **Number of visits to Emergency department within preceding 6 months** 0123≥4 | 01234 |

NOTE: Adapted from van Walraven C, Dhalla IA, Bell C, et al. Derivation and validation of an index to predict early death or unplanned readmission after discharge from hospital to the community. *CMAJ*. 2010;182(6):551-557.

**Supplemental Table 1B.** HOSPITAL Score

|  |  |  |
| --- | --- | --- |
|  | **Attribute** | **Points** |
| H | Low hemoglobin level at discharge (<12 g/dL)  | 1 |
| O | Active diagnosis of cancera | 2 |
| S | Low sodium level at discharge (<135 mmol/L ) | 1 |
| P | Any *ICD-9-CM* coded procedure during hospital stay | 1 |
| IT | Index admission type: nonelective | 1 |
| A | Number of hospital admissions within preceding year01-5>5 | 025 |
| L | Length of stay ≥8 daysa | 2 |

NOTE: Adapted from Donzé J, Aujesky D, Williams D, Schnipper JL. Potentially avoidable 30-day hospital readmissions in medical patients: derivation and validation of a prediction model. *JAMA Intern Med*. 2013;173(8):632-638. Abbreviation: *ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification*.

a Because there was no oncology service in the department, “discharge from an oncology service” was replaced with “active diagnosis of cancer”. We also tailored the attribute “length of stay” to the median in Switzerland (8 days instead of 5 days). This adapted version was previously validated in this same cohort of patients (Aubert CE, Folly A, Mancinetti M, Hayoz D, Donzé J. Prospective validation and adaptation of the HOSPITAL score to predict high risk of unplanned readmission of medical patients. *Swiss Med Wkly*. 2016;146:w14335).

**Supplemental Table 2.** Univariate and Multivariate Logistic Regression for Unplanned Readmission or Death Within 30 Days After Discharge, With Differences Between Admission and Discharge Biomarker Levels Used as Predictive Variables

|  |  |  |  |
| --- | --- | --- | --- |
| **Difference in Biomarker Levels Between Admission and Dischargea** | **Univariate Analysis****OR (95% CI)** | **Model Ac****OR (95% CI)** | **Model Bd****OR (95% CI)** |
| Δ ADM  | 1.31 (0.59, 2.90) | 1.37 (0.62, 3.04) | 1.45 (0.67, 3.12) |
| Δ copeptin  | 1.01 (0.99, 1.03) | 1.01 (0.99, 1.03) | 1.01 (0.99, 1.03) |
| Δ cortisolb | 1.00 (1.00, 1.00) | 1.00 (1.00, 1.00) | 1.00 (1.00, 1.00) |
| Δ prolactin  | 1.01 (0.99, 1.02) | 1.01 (0.99, 1.03) | 1.01 (0.99, 1.03) |

NOTE: Abbreviations: ADM, midregional pro-adrenomedullin; CI, confidence interval; OR, odds ratio.

a Difference between admission and discharge levels (admission level minus discharge level).

b Patients who had systemic corticosteroid therapy before or during hospitalization were excluded (n = 105).

c Model A adjusted for age and LACE index.

d Model Badjusted for age and HOSPITAL score.

**Supplemental Table 3.** Multivariate Logistic Regression for Unplanned Readmission or Death Within 30 Days After Discharge

|  |  |  |
| --- | --- | --- |
| **Biomarker** | **Model Ac****OR (95% CI)** | **Model Bd****OR (95% CI)** |
| **ADM, >2 nmol/La**Age LACE indexHOSPITAL score | 2.34 (0.87, 6.33)0.97 (0.94, 1.01)1.09 (0.93, 1.28)— | 2.39 (0.88, 6.50)0.97 (0.94, 1.01)—1.19 (1.04, 1.36) |
| **Copeptin, >9 pmol/La**Age LACE indexHOSPITAL score | 2.72 (1.30, 5.69)0.97 (0.94, 1.00)1.08 (0.92, 1.26)— | 2.69 (1.29, 5.64)0.97 (0.94, 1.00)—1.18 (1.03, 1.35) |
| **Cortisol, >590 nmol/La,b**Age LACE indexHOSPITAL score | 3.82 (1.54, 9.43)0.99 (0.95, 1.03)1.08 (0.87, 1.34)— | 3.43 (1.36, 8.65)0.99 (0.95, 1.03)—1.18 (0.98, 1.41) |
| **Prolactin, >23 μg/La**Age LACE indexHOSPITAL score | 1.86 (0.83, 4.13)0.97 (0.94, 1.01)1.10 (0.94, 1.28)— | 1.78 (0.79, 3.98)0.98 (0.95, 1.01)—1.18 (1.04, 1.36) |

NOTE: Abbreviations: ADM, midregional pro-adrenomedullin; CI, confidence interval; OR, odds ratio.

a Cutoff levels: best compromise between sensitivity and specificity, identified by receiver operating characteristic curves analysis. Levels are at discharge.

b Patients who had systemic corticosteroid therapy before or during hospitalization were excluded (n = 105).

c Model A adjusted for age and LACE index.

d Model B adjusted for age and HOSPITAL score.

**Supplemental Table 4.** Multivariate Logistic Regression for Unplanned Readmission or Death Within 90 Days After Discharge

|  |  |  |
| --- | --- | --- |
| **Biomarker** | **Model Ac****OR (95% CI)** | **Model Bd****OR (95% CI)** |
| **ADM, >2 nmol/La**Age LACE indexHOSPITAL score | 2.45 (1.08, 5.53)0.96 (0.94, 0.98)1.27 (1.13, 1.44)— | 2.76 (1.18, 6.47)0.96 (0.94, 0.99)—1.46 (1.29, 1.64) |
| **Copeptin, >9 pmol/La**Age LACE indexHOSPITAL score  | 2.58 (1.50, 4.43)0.96 (0.93, 0.98)1.26 (1.12, 1.43)— | 2.76 (1.56, 4.88)0.96 (0.94, 0.99)—1.44 (1.28, 1.63) |
| **Cortisol, >590 nmol/La,b**Age LACE indexHOSPITAL score | 2.35 (1.15, 4.87)0.97 (0.94, 1.01)1.18 (1.00, 1.40)— | 1.96 (0.92, 4.19)0.97 (0.94, 1.01)—1.40 (1.19, 1.64) |
| **Prolactin, >23 μg/La**Age LACE indexHOSPITAL score | 1.58 (0.84, 2.99)0.96 (0.94, 0.98)1.28 (1.13, 1.44)— | 1.49 (0.76, 2.89)0.97 (0.94, 0.99)—1.44 (1.27, 1.62) |

NOTE: Abbreviations: ADM, midregional pro-adrenomedullin; CI, confidence interval; OR, odds ratio.

a Cutoff levels: best compromise between sensitivity and specificity, identified by receiver operating characteristic curves analysis. Levels are at discharge.

b Patients who had systemic corticosteroid therapy before or during hospitalization were excluded (n = 105).

c Model A adjusted for age and LACE index.

d Model B adjusted for age and HOSPITAL score.

**Supplemental Table 5.** HOSPITAL Score and LACE Index in Their Original Versions and After Addition of ADM, Copeptin, Cortisol, and Prolactin, Respectively: Discrimination, Calibration, and Net Reclassification Improvement

|  |  |
| --- | --- |
|  | **HOSPITAL Score** |
|  | **Original** | **+ADM >2 nmol/L**  | **+Copeptin >9 pmol/L** | **+Cortisol >590 nmol/L** | **+Prolactin >23 μg/L** |
| AUROC (95% CI) | 0.70 (0.60, 0.80) | 0.72 (0.62, 0.81) | 0.74 (0.65, 0.83) | 0.76 (0.65, 0.86) | 0.72 (0.62, 0.81) |
| *P* for difference in AUROC | Reference | 0.33 | 0.15 | 0.19 | 0.37 |
| Hosmer-Lemeshow goodness-of-fit test (*P*) | 0.80 | 0.47 | 0.39 | 0.92 | 0.11 |
| NRIevent (95% CI) | Reference | –0.67 (–0.74, 0.57) | 0.28 (–0.03, 0.58) | 0.09 (–0.37, 0.50) | –0.33 (–0.61, 0.58) |
| NRInonevent (95% CI) | Reference | 0.74 (–0.51, 0.82) | 0.19 (0.07, 0.32) | 0.53 (0.26, 0.62) | 0.63 (–0.61, 0.58) |
| NRIoverall (95% CI) | Reference | 0.07 (–0.23, 0.53) | 0.47 (0.13, 0.79) | 0.62 (–0.11, 1.04) | 0.30 (–0.34, 0.56) |
|  | **LACE Index** |
|  | **Original** | **+ADM >2 nmol/L**  | **+Copeptin >9 ρmol/L** | **+Cortisol >590 nmol/L** | **+Prolactin >23 μg/L** |
| AUROC (95% CI) | 0.59 (0.49, 0.68) | 0.62 (0.53, 0.72) | 0.66 (0.58, 0.75) | 0.69 (0.57, 0.80) | 0.63 (0.53, 0.73) |
| *P* for difference in AUROC | Reference | 0.24 | 0.08 | 0.04 | 0.19 |
| Hosmer-Lemeshow goodness-of-fit test (*P*) | 0.71 | 1.00 | 0.68 | 0.71 | 0.90 |
| NRIevent (95% CI) | Reference | –0.67 (–0.78, 0.86) | 0.28 (–0.18, 0.61) | 0.09 (–0.38, 0.50) | –0.44 (–0.68, 0.71) |
| NRInonevent (95% CI) | Reference | 0.75 (–0.69, 0.79) | 0.19 (0.01, 0.31) | 0.53 (0.37, 0.64) | 0.66 (–0.62, 0.73) |
| NRIoverall (95% CI) | Reference | 0.08 (–0.35, 0.38) | 0.47 (–0.10, 0.82) | 0.62 (0.15, 1.06) | 0.21 (–0.38, 0.54) |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| NRIevent (95% CI) | Reference | –0.67 (–0.78, 0.86) | 0.28 (–0.18, 0.61) | 0.09 (–0.38, 0.50) | –0.44 (–0.68, 0.71) |
| NRInonevent (95% CI) | Reference | 0.75 (–0.69, 0.79) | 0.19 (0.01, 0.31) | 0.53 (0.37, 0.64) | 0.66 (–0.62, 0.73) |
| NRIoverall (95% CI) | Reference | 0.08 (–0.35, 0.38) | 0.47 (–0.10, 0.82) | 0.62 (0.15, 1.06) | 0.21 (–0.38, 0.54) |

NOTE: To avoid a biased comparison, we included only patients with available data for all 4 biomarkers (n = 316). For the cortisol analysis, we excluded 105 patients who had systemic cortiscosteroid therapy before or during hospitalization. Cutoff levels for biomarkers were defined as best compromise between sensitivity and specificity, identified by receiver operating characteristic curves analysis. Levels are at discharge. Abbreviations: ADM, midregional pro-adrenomedullin; AUROC, area under the receiver operating characteristic curve; CI, confidence interval; NRI, Net Reclassification Index.