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Risk stratification in emergency medicine: towards improved age and sex adjusted risk assessment

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SUMMARY

11.1 SUMMARY

Chapter 1 describes the background and aims of this thesis. The growing number of older patients presenting to Emergency Departments (EDs) requires better risk stratification to guide treatment and disposition decisions. Therefore, it is essential to understand the effect of age on the associations between physiological variables and outcomes.

More importantly, most risk tools are not age or sex adjusted and are not based on a statistical approach. An age and sex adjusted risk tool could improve risk stratification in the ED.

This thesis is divided into three parts and has four aims, regarding age-adjusted interpretation of physiological variables for risk stratification in ED patients, developing a new age- and sex-adjusted risk tool for the hospital, and describing potential bias if risk tools are used for comparing the quality of care among departments.

11.2 PART I

Age and sex adjusted interpretation of physiological variables in Emergency Department patients

In **Chapter 2 and 3**, we studied the associations between vital signs, biomarkers and relevant clinical outcomes in ED patients of different age categories. Data from the Netherlands Emergency department Evaluation Database (NEED) were used including patients ≥ 18 years.

The risk for mortality increased gradually with decreasing SBP and decreasing peripheral oxygen saturation (SpO_2). Diastolic blood pressure (DBP), mean arterial pressure (MAP) and heart rate (HR) had quasi-U-shaped associations with mortality. Mortality did not increase for temperatures anywhere in the range between 35.5-42.0°C, with a single cut-off around 35.5°C below which mortality increased. Single cut-offs were also found for MAP < 70 mmHg and respiratory rate > 22 /min.. However, using these single cut-offs would ignore the further risk increase with more extreme values of these vital signs. For all vital signs, older patients had larger increases in absolute mortality compared to younger patients.

Mortality increased gradually for increasing C-reactive Protein (CRP), and had a U-shaped association for creatinine, sodium, leukocytes, and hemoglobin. Age significantly affected the associations between most studied blood tests and mortality.

In summary, the use of a single cut-off for each physiological variable in risk stratification tools and acute care guidelines deserves scrutiny. The association between blood tests and (adjusted) mortality depends on age. Risk tools should consider using age-adjusted numerical scores.

In **Chapter 4** we assessed how often baseline systolic blood pressure (SBP) could be retrieved from the Electronic Health Record (EHR) in older ED patients, and whether the difference between the baseline SBP and initial SBP in the ED (Δ SBP) was associated with 30-day mortality. In two Dutch EDs, baseline SBPs were found in 220 out of 300 patients (73.3%). In 72 patients with normal initial SBPs in the ED, fifteen had a negative Δ SBP with 20% mortality. A negative Δ SBP was associated with 30-day mortality (AHR 4.7; 95%-CI 1.7-12.7).

Baseline SBPs are often available in older ED patients. The Δ SBP has prognostic value and may be used as an extra variable to recognize hypotension.

Chapter 5 describes sex differences regarding disease presentations, disease severity and case-mix adjusted outcomes in the ED. The NEED was used as a data source.

Patient characteristics at ED presentation and diagnoses were comparable between sexes. In-hospital mortality was higher for males at 2.2% compared to 1.7% for females. Males had a higher adjusted risk for mortality (AOR 1.34; 95%-CI 1.24-1.46) and for high dependency care unit admission (1.46; 95%-CI 1.37-1.56). This higher risk was present for all triage categories and almost all presenting complaints.

Sex-adjusted risk scores may improve risk stratification in the ED.

In **Chapter 6** we assessed the association between SBP and heart rate (HR) in ED patients of different age categories. The NEED was used as a data source and a cohort including patients with a suspected infection. Findings were validated in a Danish Multicenter Cohort (DMC).

No clinically relevant unadjusted or adjusted associations were found between SBP and HR in any age category or subgroup of ED patients. No increase in HR existed with a decreasing SBP during ED treatment in ED patients with a suspected infection.

In conclusion, no clinically relevant association existed between SBP and HR in ED patients of any age category, neither in subgroups nor in a different international setting. As a result, hypotension and shock cannot be recognized solely by tachycardia.

11.3 PART II

Development and external validation of an age and sex adjusted Early Warning Score

In **Chapter 7** we investigated how age affects the predictive performance of the National Early Warning Score. The DMC was used as a development cohort including 14,809 patients ≥ 18 years. External validation was performed in the NEED.

For NEWS alone, severe underestimation of risk was observed for persons >80 while overall Area Under Receiver Operating Characteristic (AUROC) was 0.82 (CI: 0.80-0.84) in the DMC and 0.75 (CI: 0.75-0.77) in the NEED. When combining NEWS with age, underestimation of risks was eliminated for persons >80 and overall AUROC increased significantly to 0.86 (CI: 0.85-0.88) in the DMC and 0.82 (CI: 0.81-0.83) in the NEED.

In summary, combining NEWS with age improved the prediction performance regarding in-hospital mortality, mostly for persons aged above 80 and can potentially improve decision policies at arrival to EDs.

In **Chapter 8** we developed and externally validated the International Early Warning Score (IEWs), a recalibrated NEWS including age and sex. The NEED was used as the development cohort and the DMC as the external validation cohort. Model performance to predict in-hospital mortality was evaluated by discrimination (AUROC), calibration curves, reclassification and clinical usefulness by decision curve analysis.

The in-hospital mortality rate was 2.4% (N=2314) in the NEED and 2.5% (N=365) in the DMC. Overall, the IEWS performed significantly better than NEWS with an AUROC of 0.89 (95% confidence Intervals (CI) 0.89-0.90) versus 0.82 (CI 0.82-0.83) in the NEED and 0.87 (CI 0.85-0.88) versus 0.82 (CI 0.80-0.84) at external validation. For each age category discrimination improved with IEWS compared to NEWS. Calibration for NEWS predictions underestimated risk in older patients and overestimated risk in the youngest, while calibration improved for IEWS with a substantial improvement of reclassification of patients from low to high risk and a standardized net benefit of 5-15% in the relevant risk range for all age categories.

In conclusion, the IEWS, a recalibrated NEWS including age and sex, substantially improves mortality prediction for all ages in ED patients. The better classification into low and high risk may potentially contribute to better decision policies and the IEWS should therefore replace NEWS in the ED in Western countries.

11.4 PART III

Bias in the use of risk tools to compare quality of care

The aim of **Chapter 9** was to assess to what extent predicted mortality risk would be affected if the Acute Physiology and Chronic Health Evaluation (APACHE)-IV score was recalculated with the initial physiological variables from the ED. Secondly, to evaluate whether ED Length of Stay (LOS) was associated with a change (delta) in these APACHE-IV scores. Data from two Dutch quality registries were linked: the NEED and the National Intensive Care Evaluation (NICE) registry.

The Standardized mortality ratio (SMR) changed from 0.63 (95%CI 0.54-0.72) to 0.55 (95%CI 0.47-0.63) if ED physiological variables were considered in calculating the APACHE-IV score. ED LOS >3.9hours was associated with a slight increase in delta APACHE-IV of 1.6 (95% CI 0.4-2.8) compared to ED LOS <1.7hours.

In summary, predicted mortality risks and SMRs calculated by the APACHE IV scores are not directly comparable in patients admitted from the ED if hospitals differ in their policy to stabilize patients in the ED before ICU admission.

11.5 PART IV

General discussion

Chapter 10 constitutes the general discussion and clinical implications of the main findings, general limitations and future perspectives.