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

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EMERGENCY

1

GENERAL INTRODUCTION

1.1 AN AGING POPULATION

Emergency departments (EDs) are fast-paced working environments with a high turnover of acutely ill patients with varying disease presentations like fractures and wounds to sepsis and cardiac arrest. Over the last several decades, older people have represented an increasing proportion of ED visits worldwide due to an aging population.[1-3] The higher proportion of elderly represents a challenge for the acute care as older people more often present with non-specific complaints of an acute illness combined with multiple comorbidities, polypharmacy, and altered mental status, complicating diagnostic work-up and treatment.[2, 4, 5] More importantly, older patients are at higher risk for hospitalization and death after an ED visit.[6] Timely clinical decisions are therefore crucial. Many clinical decisions in the ED are based on the patients' risk and prognosis. Risk stratification is the process of assigning a risk status to patients, then using this information to direct care to improve overall health outcomes. As risk stratification enables clinicians to identify the right level of care and services for emergency patients, it may also help to prevent overcrowding through early disposition decisions. Risk stratification forms therefore the backbone of Emergency Medicine.

1.2 RISK STRATIFICATION

Until the 20th Century, risk stratification or prognostication was the major task of the medical profession before treatment options such as antibiotics existed. Doctors made the clinical diagnosis of pneumonia not because they were able to treat it, but only to prognosticate so they could inform the family to settle their affairs, as pneumonia used to be the main cause of death. After a rapid grow in medical developments, prognostication received almost no more attention in medical textbooks by 1970 due to a shift from prognostication to a diagnosis-based concept focused on diagnosis and therapy.[7] Explicit attention to prognosis consequently diminished and became an intrinsic part of diagnosis and therapy. Nowadays, in the day-to-day practice of medicine, clinicians are continuously making risk assessments by relying on their estimates of severity to make clinical decisions.[8] This is either done by intuitive, gestalt-based assessments or with the help of formal risk scores. In both ways, the clinician estimates the risk for adverse outcomes or deterioration based on a few or many physiological variables. Vital signs are the most important objective physiological variables used to assess the severity of illness,[9, 10] and abnormal vital signs are associated with poor outcomes.[11] However, age-related changes may affect the interpretation and use of vital signs during risk assessment. Thus, physiological variables may need different interpretations in older patients because of (patho)-

physiological changes with increasing age. For example, arterial walls become stiffer, causing higher blood pressure variability, and heart rate response to stress may be blunted.[12] Laboratory tests, or biomarkers, can also be used for risk assessment, but their normal values may also change with increasing age. For correct risk stratification, it is therefore important that clinicians understand the relationship between these physiological parameters and outcomes in both young and old patients.

1.3 SEX DIFFERENCES

Besides age differences in the ED, physicians have become more aware of sex differences in acute diseases, especially after the apparent sex differences in clinical outcomes during the Coronavirus Disease 2019 (COVID-19) pandemic.[13] Male patients had almost three times the odds of Intensive Care Unit (ICU) admission and 1.4 times higher odds of death with COVID-19.[13] Nonetheless, these outcome differences between men and women are not solely described for COVID-19. Sex differences in outcomes and clinical presentations have been described in many diseases, such as acute myocardial infarction, stroke, and infectious diseases.[14-20] Nonetheless, it remains unclear whether male sex is an independent risk factor for adverse outcomes in the overall ED population or if the higher risk in males is caused by higher disease severity at ED presentation. If healthcare providers are aware of sex differences in disease presentations and clinical outcomes, they may be able to better anticipate the clinical course and provide better treatment choices for both men and women. If male sex is a risk factor for poor outcomes in the ED, clinicians should incorporate this variable in their risk assessment.

1.4 RISK TOOLS

Many risk stratification tools have been introduced in the Emergency Department, such as Early Warning Scores (EWSs), the quick-sequential organ failure assessment score (qSOFA) for sepsis, the CURB-65 for pneumonia, and the Revised Trauma Score (RTS) for trauma patients.[21-26] Most scores detect clinical deterioration or predict mortality for all patients or subgroups. These scores were designed to support clinical intuition and gestalt by providing a formal risk score. Nonetheless, many risk scores have limited predictive performance in older patients.[27] This poor performance may be caused by relevant age differences in risk which are often not considered while developing these scores. Moreover, many scores use single thresholds for physiological variables (i.e., higher, or lower than a systolic blood pressure of 90mmHg), suggesting a clinically relevant change

in prognosis at this threshold. Also, using one threshold indicates that one cut-off may discriminate between a good and bad prognosis. However, recent studies in patients with traumatic brain injury and sepsis showed that prognosis linearly worsens with decreasing systolic blood pressure (SBP), without a single identifiable threshold.[28, 29] Similarly, linear, or U-shaped instead of dichotomous associations may exist for other vital signs used in ED risk stratification. Although most EWSs use multiple thresholds for each physiological variable, they were not developed by applying statistical methods but rather by clinical consensus.[10, 30] Using scores that are not age and sex-adjusted with erroneously selected thresholds may negatively affect patient care if used for clinical guidance. This may especially apply to the ED where patients are often undifferentiated and at risk for deterioration. An example of an excellent clinical score is the Acute Physiology and Chronic Health Evaluation 4th edition (APACHE-IV) used for Intensive Care Unit (ICU) patients.[31, 32] The APACHE-IV has excellent discriminative performance and calibration for ICU patients, not only allowing to predict accurately the outcome for an individual patient, but also allowing to compare the quality of care of ICUs by calculating a Standardized Mortality Ratio (SMR). The SMR is the observed mortality in ICU patients divided by the predicted mortality. An SMR below 1 implies fewer people died after ICU admission than predicted, suggesting good quality of care. However, although this score is an excellent prediction tool, other factors may lead to a higher calculated SMR. For example, physiological parameters may improve or deteriorate in the hours before ICU admission,[33-36] e.g., during initial treatment in the emergency department (ED). These data measured before ICU admission are not included in the original APACHE-IV score.[31, 32] Consequently, the calculated severity of illness and predicted mortality risk may differ when the same initial treatment is provided before or after ICU admission for a given patient.[37, 38] It is essential to understand the effect of ED treatment and clinical course on the predicted mortality risk calculated by the APACHE-IV, if these scores are used to compare the quality of care among departments or hospitals.

1.5 THE NETHERLANDS EMERGENCY DEPARTMENT EVALUATION DATABASE (NEED)

This thesis used the Netherlands Emergency department Evaluation Database (NEED) to investigate the aims of this thesis. The NEED is the national quality registry for EDs in the Netherlands, founded in 2016, and aims to contribute to the transparency and quality of ED care in the Netherlands by providing reliable data to the participating EDs (www.stichting-need.nl). Participating EDs receive twice a year a report for

benchmarking in which the data of the hospital are compared with the pooled data of all participating EDs in the NEED.

1.6 AIM OF THE THESIS

This thesis has four aims. First, to investigate whether the interpretation of physiological variables should be age and sex adjusted for ED patients. The second aim is to assess whether thresholds for vital signs and biomarkers truly exist. The third aim is to develop and externally validate an age and sex adjusted Early Warning Score and assess whether this score improves the classification of ED patients into low, intermediate, and high risk. The fourth aim is to evaluate the effect of initial ED treatment versus immediate ICU admission on predicted mortality risk and SMR in critically ill patients.

1.7 OUTLINE OF THE THESIS

This thesis is divided into three parts. The first part includes the first and second aim of this thesis. In **chapter 2,** we study the association between vital signs and clinical outcomes in ED patients of different age categories. In **chapter 3,** we evaluate the effect of age on the interpretation of biomarkers of renal function and homeostasis, inflammation, and circulation in ED patients. In **chapter 4,** we investigate whether the difference between the patients' initial and previously measured systolic blood pressure (delta SBP) predicts mortality in older ED patients. In **Chapter 5,** we study sex differences in clinical presentation and risk stratification in the ED. In **Chapter 6,** the association between SBP and heart rate (HR) is investigated.

The second part of this thesis is devoted to developing an age and sex adjusted EWS. **Chapter 7** describes the effect of including age in the National Early Warning Score (NEWS) on its predictive performance in different age categories. In **Chapter 8,** we develop and externally validate an age and sex-adjusted International Early Warning Score (IEWS).

The third part of this thesis includes one chapter, **Chapter 9**, in which we study the effect of treatment and clinical course during ED stay on severity scoring and predicted mortality risk in ICU patients.

Finally, in **chapter 10,** the main conclusions of this thesis are summarized and discussed, and future perspectives are proposed.