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

Candel, B.G.J.

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APPENDIXES

REFERENCES

1. Xu KT, Nelson BK, Berk S. The changing profile of patients who used emergency department services in the United States: 1996 to 2005. *Ann Emerg Med.* 2009;54(6):805-10. e7.
2. Samaras N, Chevalley T, Samaras D, Gold G. Older patients in the emergency department: a review. *Ann Emerg Med.* 2010;56(3):261-9.
3. Roberts DC, McKay MP, Shaffer A. Increasing rates of emergency department visits for elderly patients in the United States, 1993 to 2003. *Ann Emerg Med.* 2008;51(6):769-74.
4. Aminzadeh F, Dalziel WB. Older adults in the emergency department: a systematic review of patterns of use, adverse outcomes, and effectiveness of interventions. *Ann Emerg Med.* 2002;39(3):238-47.
5. George G, Jell C, Todd B. Effect of population ageing on emergency department speed and efficiency: a historical perspective from a district general hospital in the UK. *Emerg Med J.* 2006;23(5):379-83.
6. Baum SA, Rubenstein LZ. Old people in the emergency room: Age-related differences in emergency department use and care. *J Am Geriatr Soc.* 1987;35(5):398-404.
7. Christakis NA. The ellipsis of prognosis in modern medical thought. *Soc Sci Med.* 1997;44(3):301-15.
8. Kellett J. Prognostication—the lost skill of medicine. *Eur J Intern Med.* 2008;19(3):155-64.
9. RoyalCollegeofPhysicians. National Early Warning Score 2. Standardizing the assessment of acute-illness severity in the NHS. National Early Warning Score (NEWS). 2012.
10. Morgan R, Lloyd-Williams F, Wright M, Morgan-Warren R. An early warning scoring system for detecting developing critical illness. 1997.
11. Ljunggren M, Castrén M, Nordberg M, Kurland L. The association between vital signs and mortality in a retrospective cohort study of an unselected emergency department population. *Scand J Trauma Resusc Emerg Med.* 2016;24(1):21.
12. Chester JG, Rudolph JL. Vital signs in older patients: age-related changes. *J Am Med Dir Assoc.* 2011;12(5):337-43.
13. Peckham H, de Gruijter NM, Raine C, et al. Male sex identified by global COVID-19 meta-analysis as a risk factor for death and ITU admission. *Nature communications.* 2020;11(1):1-10.
14. McGregor AJ, Beauchamp GA, Wira III CR, Perman SM, Safdar B. Sex as a biological variable in emergency medicine research and clinical practice: a brief narrative review. *West J Emerg Med.* 2017;18(6):1079.
15. Coventry LL, Finn J, Bremner AP. Sex differences in symptom presentation in acute myocardial infarction: a systematic review and meta-analysis. *Heart Lung.* 2011;40(6):477-91.
16. Reeves MJ, Bushnell CD, Howard G, et al. Sex differences in stroke: epidemiology, clinical presentation, medical care, and outcomes. *The Lancet Neurology.* 2008;7(10):915-26.
17. Washington DL, Bird CE. Sex differences in disease presentation in the emergency department. *Ann Emerg Med.* 2002;40(5):461-3.

18. Hubert H, Jaeger D, Baert V, et al. Effect of gender on out-of-hospital cardiac arrest survival: a registry-based study. *Eur J Emerg Med.* 2021;28(1):50-7.
19. Blom MT, Oving I, Berdowski J, van Valkengoed IG, Bardai A, Tan HL. Women have lower chances than men to be resuscitated and survive out-of-hospital cardiac arrest. *Eur Heart J.* 2019;40(47):3824-34.
20. Wenham C, Smith J, Morgan R. COVID-19: the gendered impacts of the outbreak. *The Lancet.* 2020;395(10227):846-8.
21. Metlay JP, Waterer GW, Long AC, et al. Diagnosis and treatment of adults with community-acquired pneumonia. An official clinical practice guideline of the American Thoracic Society and Infectious Diseases Society of America. *Am J Respir Crit Care Med.* 2019;200(7):e45-e67.
22. Bone RC. Immunologic dissonance: a continuing evolution in our understanding of the systemic inflammatory response syndrome (SIRS) and the multiple organ dysfunction syndrome (MODS). *Ann Intern Med.* 1996;125(8):680-7.
23. Champion HR, Sacco WJ, Copes WS, Gann DS, Gennarelli TA, Flanagan ME. A revision of the Trauma Score. *The Journal of trauma.* 1989;29(5):623-9.
24. Shapiro NI, Wolfe RE, Moore RB, Smith E, Burdick E, Bates DW. Mortality in Emergency Department Sepsis (MEDS) score: a prospectively derived and validated clinical prediction rule. *Crit Care Med.* 2003;31(3):670-5.
25. Seymour CW, Liu VX, Iwashyna TJ, et al. Assessment of clinical criteria for sepsis: for the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA.* 2016;315(8):762-74.
26. Gilpin D, Nelson P. Revised trauma score: a triage tool in the accident and emergency department. *Injury.* 1991;22(1):35-7.
27. de Groot B, Stolwijk F, Warmerdam M, et al. The most commonly used disease severity scores are inappropriate for risk stratification of older emergency department sepsis patients: an observational multi-centre study. *Scand J Trauma Resusc Emerg Med.* 2017;25(1):91.
28. Spaite DW, Hu C, Bobrow BJ, et al. Mortality and prehospital blood pressure in patients with major traumatic brain injury: implications for the hypotension threshold. *JAMA surgery.* 2017;152(4):360-8.
29. Warmerdam M, Baris L, van Liebergen M, et al. The association between systolic blood pressure and in-hospital mortality in older emergency department patients who are hospitalised with a suspected infection. *Emerg Med J.* 2018;emermed-2018-207502.
30. Prytherch DR, Smith GB, Schmidt PE, Featherstone PI. ViEWS—towards a national early warning score for detecting adult inpatient deterioration. *Resuscitation.* 2010;81(8):932-7.
31. Knaus WA, Wagner DP, Draper EA, et al. The APACHE III prognostic system: risk prediction of hospital mortality for critically ill hospitalized adults. *Chest.* 1991;100(6):1619-36.
32. Zimmerman JE, Kramer AA, McNair DS, Malila FM. Acute Physiology and Chronic Health Evaluation (APACHE) IV: hospital mortality assessment for today's critically ill patients. *Crit Care Med.* 2006;34(5):1297-310.
33. Buist M, Bernard S, Nguyen TV, Moore G, Anderson J. Association between clinically abnormal observations and subsequent in-hospital mortality: a prospective study. *Resuscitation.* 2004;62(2):137-41.

34. Considine J, Jones D, Bellomo R. Emergency department rapid response systems: the case for a standardized approach to deteriorating patients. *Eur J Emerg Med*. 2013;20(6):375-81.
35. Flabouris A, Hart GK, George C. Outcomes of patients admitted to tertiary intensive care units after interhospital transfer: comparison with patients admitted from emergency departments. *Crit Care Resusc*. 2008;10(2):97-105.
36. Simpson H, Clancy M, Goldfrad C, Rowan K. Admissions to intensive care units from emergency departments: a descriptive study. *Emerg Med J*. 2005;22(6):423-8.
37. Dragsted L, Jørgensen J, Jensen N-H, et al. Interhospital comparisons of patient outcome from intensive care: importance of lead-time bias. *Crit Care Med*. 1989;17(5):418-22.
38. Tunnell R, Millar B, Smith G. The effect of lead time bias on severity of illness scoring, mortality prediction and standardised mortality ratio in intensive care—a pilot study. *Anaesthesia*. 1998;53(11):1045-53.
39. Rhodes A, Evans LE, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. *Intensive Care Med*. 2017;43(3):304-77.
40. American College of S, Committee on T. ATLS : advanced trauma life support for doctors : student course manual. Chicago, IL: American College of Surgeons; 2008.
41. Adams Jr HP, Del Zoppo G, Alberts MJ, et al. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: the American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. *Stroke*. 2007;38(5):1655-711.
42. Pirneskoski J, Lääperi M, Kuisma M, Olkkola KT, Nurmi J. Ability of prehospital NEWS to predict 1-day and 7-day mortality is reduced in the older adult patients. *Emerg Med J*. 2021.
43. Cretikos MA, Bellomo R, Hillman K, Chen J, Finfer S, Flabouris A. Respiratory rate: the neglected vital sign. *Med J Aust*. 2008;188(11):657-9.
44. Vittinghoff E, McCulloch CE. Relaxing the rule of ten events per variable in logistic and Cox regression. *Am J Epidemiol*. 2007;165(6):710-8.
45. van der Veen D, Heringhaus C, de Groot B. Appropriateness, Reasons and Independent Predictors of Consultations in the Emergency Department (ED) of a Dutch Tertiary Care Center: A Prospective Cohort Study. *PLoS One*. 2016;11(2):e0149079.
46. Woods RA, Lee R, Ospina MB, et al. Consultation outcomes in the emergency department: exploring rates and complexity. *Canadian Journal of Emergency Medicine*. 2008;10(1):25-31.
47. Rubulotta F, Marshall JC, Ramsay G, Nelson D, Levy M, Williams M. Predisposition, insult/infection, response, and organ dysfunction: A new model for staging severe sepsis. *Crit Care Med*. 2009;37(4):1329-35.
48. Lim WS, Van der Eerden M, Laing R, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. *Thorax*. 2003;58(5):377-82.

49. Klang E, Soffer S, Shimon Shahar M, et al. Association of normal systolic blood pressure in the emergency department with higher in-hospital mortality among hypertensive patients. *The Journal of Clinical Hypertension*. 2019;21(12):1841-8.
50. Kristensen AKB, Holler JG, Mikkelsen S, Hallas J, Lassen A. Systolic blood pressure and short-term mortality in the emergency department and prehospital setting: a hospital-based cohort study. *Critical Care*. 2015;19(1):158.
51. Alam N, Hobbelink EL, van Tienhoven A-J, van de Ven PM, Jansma EP, Nanayakkara PW. The impact of the use of the Early Warning Score (EWS) on patient outcomes: a systematic review. *Resuscitation*. 2014;85(5):587-94.
52. Morgan R, Wright M. In defence of early warning scores. *Br J Anaesth*. 2007;99(5):747-8.
53. Oyetunji TA, Chang DC, Crompton JG, et al. Redefining hypotension in the elderly: normotension is not reassuring. *Arch Surg*. 2011;146(7):865-9.
54. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med*. 1985;13(10):818-29.
55. de Groot B, de Deckere ER, Flameling R, Sandel MH, Vis A. Performance of illness severity scores to guide disposition of emergency department patients with severe sepsis or septic shock. *Eur J Emerg Med*. 2012;19(5):316-22.
56. Lemeshow S, Teres D, Klar J, Avrunin JS, Gehlbach SH, Rapoport J. Mortality Probability Models (MPM II) based on an international cohort of intensive care unit patients. *JAMA*. 1993;270(20):2478-86.
57. Howell MD, Talmor D, Schuetz P, Hunziker S, Jones AE, Shapiro NI. Proof of principle: the predisposition, infection, response, organ failure sepsis staging system. *Crit Care Med*. 2011;39(2):322-7.
58. Hall M, Bebb OJ, Dondo TB, et al. Guideline-indicated treatments and diagnostics, GRACE risk score, and survival for non-ST elevation myocardial infarction. *Eur Heart J*. 2018;39(42):3798-806.
59. Leppäniemi A, Tolonen M, Tarasconi A, et al. 2019 WSES guidelines for the management of severe acute pancreatitis. *World J Emerg Surg*. 2019;14(1):27.
60. van Bommel T, Woittiez K, Blauw GJ, et al. Prospective study of the effect of blood pressure on renal function in old age: the Leiden 85-Plus Study. 2006;17(9):2561-6.
61. Epstein M. Aging and the kidney. *J Am Soc Nephrol*. 1996;7(8):1106.
62. den Elzen WP, Brouwer N, Thelen MH, et al. NUMBER: standardized reference intervals in the Netherlands using a 'big data' approach. 2018;57(1):42-56.
63. Raven W, van den Hoven EM, Gaakeer MI, et al. The association between presenting complaints and clinical outcomes in emergency department patients of different age categories. *European Journal of Emergency Medicine: Official Journal of the European Society for Emergency Medicine*. 2021.
64. Wood SN. Generalized additive models: an introduction with R: CRC press; 2017.
65. Mohammed MA, Rudge G, Wood G, et al. Which is more useful in predicting hospital mortality-dichotomised blood test results or actual test values? A retrospective study in two hospitals. *PLoS One*. 2012;7(10):e46860.
66. Pedersen PB, Henriksen DP, Brabrand M, Lassen AT. Level of vital and laboratory values on arrival, and increased risk of 7-day mortality among adult patients in the emergency department: a population-based cohort study. *BMJ Open*. 2020;10(11):e038516.

67. Asadollahi K, Hastings IM, Gill GV, Beeching NJ. Prediction of hospital mortality from admission laboratory data and patient age: a simple model. *Emerg Med Australas*. 2011;23(3):354-63.
68. Froom P, Shimoni Z. Prediction of hospital mortality rates by admission laboratory tests. *Clin Chem*. 2006;52(2):325-8.
69. Tabak YP, Sun X, Nunez CM, Johannes RS. Using electronic health record data to develop inpatient mortality predictive model: Acute Laboratory Risk of Mortality Score (ALaRMS). *J Am Med Inform Assoc*. 2014;21(3):455-63.
70. Kristensen M, Iversen AKS, Gerds TA, et al. Routine blood tests are associated with short term mortality and can improve emergency department triage: a cohort study of > 12,000 patients. *Scand J Trauma Resusc Emerg Med*. 2017;25(1):115.
71. Prytherch D, Sirl J, Schmidt P, Featherstone PI, Weaver P, Smith GB. The use of routine laboratory data to predict in-hospital death in medical admissions. *Resuscitation*. 2005;66(2):203-7.
72. Redfern OC, Pimentel MA, Prytherch D, et al. Predicting in-hospital mortality and unanticipated admissions to the intensive care unit using routinely collected blood tests and vital signs: Development and validation of a multivariable model. *Resuscitation*. 2018;133:75-81.
73. Jarvis SW, Kovacs C, Badriyah T, et al. Development and validation of a decision tree early warning score based on routine laboratory test results for the discrimination of hospital mortality in emergency medical admissions. *Resuscitation*. 2013;84(11):1494-9.
74. Brabrand M, Knudsen T, Hallas J. Identifying admitted patients at risk of dying: a prospective observational validation of four biochemical scoring systems. *BMJ open*. 2013;3(6).
75. Silke B, Kellett J, Rooney T, Bennett K, O'riordan D. An improved medical admissions risk system using multivariable fractional polynomial logistic regression modelling. *QJM: An International Journal of Medicine*. 2010;103(1):23-32.
76. Lindner G, Pfortmüller CA, Leichtle AB, Fiedler GM, Exadaktylos AK. Age-related variety in electrolyte levels and prevalence of dysnatremias and dyskalemias in patients presenting to the emergency department. *Gerontology*. 2014;60(5):420-3.
77. Nilsson-Ehle H, Jagenburg R, Landahl S, Svanborg A. Blood haemoglobin declines in the elderly: implications for reference intervals from age 70 to 88. *Eur J Haematol*. 2000;65(5):297-305.
78. Roenhoej R, Hasselbalch RB, Schultz M, et al. Abnormal routine blood tests as predictors of mortality in acutely admitted patients. *Clin Biochem*. 2020;77:14-9.
79. Lloyd-Sherlock P, Beard J, Minicuci N, Ebrahim S, Chatterji S. Hypertension among older adults in low-and middle-income countries: prevalence, awareness and control. *International journal of epidemiology*. 2014;43(1):116-28.
80. Kaplan MS, Huguet N, Feeny DH, McFarland BH. Self-reported hypertension prevalence and income among older adults in Canada and the United States. *Social science & medicine*. 2010;70(6):844-9.
81. Kalra D. Medicine in Europe: Electronic health records: the European scene. *BMJ*. 1994;309(6965):1358-61.

82. Candel BG, Duijzer R, Gaakeer MI, de Jonge E, de Groot B. The association between vital signs and relevant clinical outcomes in emergency department patients of different age categories. *Emerg Med J*. 2022;39(12):903-11.
83. Futier E, Lefrant J-Y, Guinot P-G, et al. Effect of individualized vs standard blood pressure management strategies on postoperative organ dysfunction among high-risk patients undergoing major surgery: a randomized clinical trial. *JAMA*. 2017;318(14):1346-57.
84. Asfar P, Meziani F, Hamel J-F, et al. High versus low blood-pressure target in patients with septic shock. *N Engl J Med*. 2014;370:1583-93.
85. Bruijns SR, Guly HR, Bouamra O, Lecky F, Wallis LA. The value of the difference between ED and prehospital vital signs in predicting outcome in trauma. *Emerg Med J*. 2014;31(7):579-82.
86. Kamata K, Abe T, Aoki M, Deshpande G, Saitoh D, Tokuda Y. Dynamic vital signs may predict in-hospital mortality in elderly trauma patients. *Medicine (Baltimore)*. 2020;99(25):e20741.
87. Arbabi S, Jurkovich GJ, Wahl WL, et al. A comparison of prehospital and hospital data in trauma patients. *Journal of Trauma and Acute Care Surgery*. 2004;56(5):1029-32.
88. Churpek MM, Adhikari R, Edelson DP. The value of vital sign trends for detecting clinical deterioration on the wards. *Resuscitation*. 2016;102:1-5.
89. Brekke IJ, Puntervoll LH, Pedersen PB, Kellett J, Brabrand M. The value of vital sign trends in predicting and monitoring clinical deterioration: A systematic review. *PLoS One*. 2019;14(1).
90. Vest JR, Gamm LD. Health information exchange: persistent challenges and new strategies. *J Am Med Inform Assoc*. 2010;17(3):288-94.
91. De Hond A, Raven W, Schinkelshoek L, et al. Machine learning for developing a prediction model of hospital admission of emergency department patients: Hype or hope? *Int J Med Inform*. 2021:104496.
92. Teubner DJ, Considine J, Hakendorf P, Kim S, Bersten AD. Model to predict inpatient mortality from information gathered at presentation to an emergency department: The Triage Information Mortality Model (TIMM). *Emerg Med Australas*. 2015;27(4):300-6.
93. Xie F, Liu N, Wu SX, et al. Novel model for predicting inpatient mortality after emergency admission to hospital in Singapore: retrospective observational study. *BMJ open*. 2019;9(9):e031382.
94. Beglinger B, Rohacek M, Ackermann S, et al. Physician's first clinical impression of emergency department patients with nonspecific complaints is associated with morbidity and mortality. *Medicine*. 2015;94(7).
95. Ha DT, Dang TQ, Tran NV, Pham TN, Nguyen ND, Nguyen TV. Development and validation of a prognostic model for predicting 30-day mortality risk in medical patients in emergency department (ED). *Sci Rep*. 2017;7(1):1-10.
96. Safdar B, Ona Ayala KE, Ali SS, et al. Inclusion of sex and gender in Emergency Medicine Research—A 2018 update. *Acad Emerg Med*. 2019;26(3):293-302.
97. van der Veen D, Remeijer C, Fogteloo AJ, Heringhaus C, de Groot B. Independent determinants of prolonged emergency department length of stay in a tertiary care centre: a prospective cohort study. *Scand J Trauma Resusc Emerg Med*. 2018;26(1):81.
98. OECDHealthStatistics. Eurostat Database. 2020.
99. Barba R, Marco J, Canora J, et al. Prolonged length of stay in hospitalized internal medicine patients. *Eur J Intern Med*. 2015;26(10):772-5.

100. Angele MK, Pratschke S, Hubbard WJ, Chaudry IH. Gender differences in sepsis: cardiovascular and immunological aspects. *Virulence*. 2014;5(1):12-9.
101. Labiche LA, Chan W, Saldin KR, Morgenstern LB. Sex and acute stroke presentation. *Ann Emerg Med*. 2002;40(5):453-60.
102. El-Menyar A, Zubaid M, Sulaiman K, et al. Atypical presentation of acute coronary syndrome: a significant independent predictor of in-hospital mortality. *J Cardiol*. 2011;57(2):165-71.
103. Sandberg K, Ji H. Sex differences in primary hypertension. *Biol Sex Differ*. 2012;3(1):1-21.
104. Backus BE, Six AJ, Kelder JC, et al. Chest pain in the emergency room: a multicenter validation of the HEART Score. *Crit Pathw Cardiol*. 2010;9(3):164-9.
105. Karounos M, Chang AM, Robey JL, et al. TIMI risk score: does it work equally well in both males and females? *Emerg Med J*. 2007;24(7):471-4.
106. Bank IE, de Hoog VC, de Kleijn DP, et al. Sex-based differences in the performance of the HEART score in patients presenting to the emergency department with acute chest pain. *Journal of the American Heart Association*. 2017;6(6):e005373.
107. Hinson JS, Martinez DA, Cabral S, et al. Triage performance in emergency medicine: a systematic review. *Ann Emerg Med*. 2019;74(1):140-52.
108. Hall JE, Hall ME. Guyton and Hall textbook of medical physiology e-Book, Ch24, 293-301: Elsevier Health Sciences; 2020.
109. Kasper D, Fauci A, Hauser S, Longo D, Jameson J, Loscalzo J. Harrison's principles of internal medicine, 19e, Chapter 232: Basic Biology of the Cardiovascular System.: McGraw-hill; 2015.
110. Subcommittee A, Group IAW. Advanced trauma life support (ATLS®): the ninth edition. *The journal of trauma and acute care surgery*. 2013;74(5):1363-6.
111. Mutschler M, Nienaber U, Brockamp T, et al. A critical reappraisal of the ATLS classification of hypovolaemic shock: does it really reflect clinical reality? *Resuscitation*. 2013;84(3):309-13.
112. Brasel KJ, Guse C, Gentilello LM, Nirula R. Heart rate: is it truly a vital sign? *Journal of Trauma and Acute Care Surgery*. 2007;62(4):812-7.
113. Guly H, Bouamra O, Little R, et al. Testing the validity of the ATLS classification of hypovolaemic shock. *Resuscitation*. 2010;81(9):1142-7.
114. Victorino GP, Battistella FD, Wisner DH. Does tachycardia correlate with hypotension after trauma? *J Am Coll Surg*. 2003;196(5):679-84.
115. Ahmad S, Tejuja A, Newman KD, Zarychanski R, Seely AJ. Clinical review: a review and analysis of heart rate variability and the diagnosis and prognosis of infection. *Critical Care*. 2009;13(6):1-7.
116. Griffin MP, O'Shea TM, Bissonette EA, Harrell FE, Lake DE, Moorman JR. Abnormal heart rate characteristics preceding neonatal sepsis and sepsis-like illness. *Pediatr Res*. 2003;53(6):920-6.
117. Valentini M, Parati G. Variables influencing heart rate. *Prog Cardiovasc Dis*. 2009;52(1):11-9.
118. Brabrand M, Hallas P, Hansen SN, Jensen KM, Madsen JLB, Posth S. Using scores to identify patients at risk of short term mortality at arrival to the acute medical unit: a validation study of six existing scores. *Eur J Intern Med*. 2017;45:32-6.

119. Nissen SK, Candel BG, Nickel CH, et al. The Impact of Age on Predictive Performance of National Early Warning Score at Arrival to Emergency Departments: Development and External Validation. *Ann Emerg Med.* 2022;79(4):354-63.
120. de Groot B, Ansems A, Gerling DH, et al. The association between time to antibiotics and relevant clinical outcomes in emergency department patients with various stages of sepsis: a prospective multi-center study. *Critical care.* 2015;19(1):1-12.
121. Goldman L, Schafer AI. *Goldman-Cecil Medicine*, 26th. Chapter 8: Cardiovascular disease. : Elsevier; 2020.
122. Secher NH, Bie P. Bradycardia during reversible haemorrhagic shock—a forgotten observation? *Clin Physiol.* 1985;5(4):315-23.
123. Oberg B, Thoren P. Increased activity in vagal cardiac afferents correlated to the appearance of reflex bradycardia during severe hemorrhage in cats. *Acta Physiol Scand.* 1970;80(4):22A-3A.
124. Castenfors J, Sjöstrand T. Circulatory Control via Vagal Afferents: I. Adjustment of heart rate to variations of blood volume in the rat. *Acta Physiol Scand.* 1972;84(3):347-54.
125. Secher N, Werner C, Warberg J, Bie P. Bradycardia during severe but reversible hypovolemic shock in man. *Circ Shock.* 1984;14(4):267-74.
126. Sander-Jensen K, Secher N, Bie P, Warberg J, Schwartz T. Vagal slowing of the heart during haemorrhage: observations from 20 consecutive hypotensive patients. *Br Med J (Clin Res Ed).* 1986;292(6517):364-6.
127. Barriot P, Riou B. Hemorrhagic shock with paradoxical bradycardia. *Intensive Care Med.* 1987;13(3):203-7.
128. Morelli A, D'Egidio A, Passariello M. Tachycardia in septic shock: pathophysiological implications and pharmacological treatment. *Annual Update in Intensive Care and Emergency Medicine 2015: Springer; 2015.* p. 115-28.
129. Parrillo JE. Pathogenetic mechanisms of septic shock. *N Engl J Med.* 1993;328(20):1471-7.
130. Gerry S, Bonnici T, Birks J, et al. Early warning scores for detecting deterioration in adult hospital patients: systematic review and critical appraisal of methodology. *BMJ.* 2020;369.
131. Physicians RCo. National Early Warning Score (NEWS) 2: standardising the assessment of acute-illness severity in the NHS. Updated report of a working party 2017. 2021.
132. RCoPo L, editor National early warning score (NEWS): standardising the assessment of acute-illness severity in the NHS—report of a working party. Royal College of Physicians; 2012.
133. Smith GB, Prytherch DR, Schmidt PE, et al. Should age be included as a component of track and trigger systems used to identify sick adult patients? *Resuscitation.* 2008;78(2):109-15.
134. LaMantia MA, Stewart PW, Platts-Mills TF, et al. Predictive value of initial triage vital signs for critically ill older adults. *West J Emerg Med.* 2013;14(5):453.
135. Subbe CP, Kruger M, Rutherford P, Gemmel L. Validation of a modified Early Warning Score in medical admissions. *QJM.* 2001;94(10):521-6.
136. Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. *Journal of British Surgery.* 2015;102(3):148-58.

137. Brabrand M, Knudsen T, Hallas J, Graham CA, Kellett J. The Paris score can reliably predict 7-day all-cause mortality for both acute medical and surgical patients: an international validation study. *QJM: An International Journal of Medicine*. 2018;111(10):721-5.
138. Nielsen MK, Henriksen DP, Østergaard KB, Dahlin J, Brabrand M. Association between presenting complaints of acutely admitted medical patients and mortality: a cohort study. *Eur J Intern Med*. 2018;54:e29-e32.
139. Öhman M, Atkins T, Cooksley T, Brabrand M. Validation of the MARS: a combined physiological and laboratory risk prediction tool for 5-to 7-day in-hospital mortality. *QJM: An International Journal of Medicine*. 2018;111(6):385-8.
140. Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol*. 2014;29(8):541-9.
141. Schmidt M, Schmidt SAJ, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol*. 2015;7:449.
142. Harrell FE. *Regression Modeling Strategies*. vol 45. Springer International Publishing, Cham2015.
143. Van Buuren S, Groothuis-Oudshoorn K. mice: Multivariate imputation by chained equations in R. *Journal of statistical software*. 2011;45:1-67.
144. Rubin DB. Inference and missing data. *Biometrika*. 1976;63(3):581-92.
145. Van Calster B, Nieboer D, Vergouwe Y, De Cock B, Pencina MJ, Steyerberg EW. A calibration hierarchy for risk models was defined: from utopia to empirical data. *J Clin Epidemiol*. 2016;74:167-76.
146. Vickers AJ, Van Calster B, Steyerberg EW. Net benefit approaches to the evaluation of prediction models, molecular markers, and diagnostic tests. *BMJ*. 2016;352.
147. Ensor J, Martin E, Riley R. Pmsampsize: calculates the minimum sample size required for developing a multivariable prediction model. 2019.
148. Heymans M, van Buuren S, Knol D, van Mechelen W, de Vet H. CW (2007). Variable selection under multiple imputation using the bootstrap in a prognostic study. *BMC Med Res Methodol*.7:33.
149. Sterne JA, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ*. 2009;338.
150. Collins GS, Moons KG. *Comparing risk prediction models*. British Medical Journal Publishing Group; 2012.
151. Lee YS, Choi JW, Park YH, et al. Evaluation of the efficacy of the National Early Warning Score in predicting in-hospital mortality via the risk stratification. *J Crit Care*. 2018;47:222-6.
152. de Groot B, Lameijer J, de Deckere ER, Vis A. The prognostic performance of the predisposition, infection, response and organ failure (PIRO) classification in high-risk and low-risk emergency department sepsis populations: comparison with clinical judgement and sepsis category. *Emerg Med J*. 2014;31(4):292-300.
153. Garwe T, Stewart K, Stoner J, et al. Out-of-hospital and inter-hospital under-triage to designated tertiary trauma centers among injured older adults: a 10-year statewide geospatial-adjusted analysis. *Prehosp Emerg Care*. 2017;21(6):734-43.

154. Schultz M, Rasmussen LJH, Carlson N, et al. Risk assessment models for potential use in the emergency department have lower predictive ability in older patients compared to the middle-aged for short-term mortality—a retrospective cohort study. *BMC Geriatr.* 2019;19(1):1-9.
155. Romero-Ortuno R, Wallis S, Biram R, Keevil V. Clinical frailty adds to acute illness severity in predicting mortality in hospitalized older adults: an observational study. *Eur J Intern Med.* 2016;35:24-34.
156. Kaeppli T, Rueegg M, Dreher-Hummel T, et al. Validation of the clinical frailty scale for prediction of thirty-day mortality in the emergency department. *Ann Emerg Med.* 2020;76(3):291-300.
157. Engvig A, Wyller TB, Skovlund E, et al. Association between clinical frailty, illness severity and post-discharge survival: a prospective cohort study of older medical inpatients in Norway. *Eur Geriatr Med.* 2022;13(2):453-61.
158. Dent E, Martin FC, Bergman H, Woo J, Romero-Ortuno R, Walston JD. Management of frailty: opportunities, challenges, and future directions. *The Lancet.* 2019;394(10206):1376-86.
159. Groenwold RH, Moons KG, Pajouheshnia R, et al. Explicit inclusion of treatment in prognostic modeling was recommended in observational and randomized settings. *J Clin Epidemiol.* 2016;78:90-100.
160. Guidet B, De Lange DW, Boumendil A, et al. The contribution of frailty, cognition, activity of daily life and comorbidities on outcome in acutely admitted patients over 80 years in European ICUs: the VIP2 study. *Intensive Care Med.* 2020;46(1):57-69.
161. Brabrand M, Kellett J, Opio M, Cooksley T, Nickel C. Should impaired mobility on presentation be a vital sign? *Acta Anaesthesiol Scand.* 2018;62(7):945-52.
162. Hillman K. Predicting outcome in the seriously ill-A new approach. 2018. p. 878-9.
163. Pencina MJ, D'Agostino Sr RB, D'Agostino Jr RB, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med.* 2008;27(2):157-72.
164. Van Calster B, McLernon DJ, Van Smeden M, Wynants L, Steyerberg EW. Calibration: the Achilles heel of predictive analytics. *BMC Med.* 2019;17(1):1-7.
165. Perel P, Prieto-Merino D, Shakur H, et al. Predicting early death in patients with traumatic bleeding: development and validation of prognostic model. *BMJ.* 2012;345.
166. Shamout F, Zhu T, Clifton L, et al. Early warning score adjusted for age to predict the composite outcome of mortality, cardiac arrest or unplanned intensive care unit admission using observational vital-sign data: a multicentre development and validation. *BMJ Open.* 2019;9(11):e033301.
167. O'Neill S, Clyne B, Bell M, et al. Why do healthcare professionals fail to escalate as per the early warning system (EWS) protocol? A qualitative evidence synthesis of the barriers and facilitators of escalation. *BMC Emerg Med.* 2021;21(1):1-19.
168. Kahneman D, Tversky A. On the psychology of prediction. *Psychol Rev.* 1973;80(4):237.
169. Smith MB, Chiovaro JC, O'Neil M, et al. Early warning system scores for clinical deterioration in hospitalized patients: a systematic review. *Annals of the American Thoracic Society.* 2014;11(9):1454-65.
170. McGinley A, Pearse RM. A national early warning score for acutely ill patients. *British Medical Journal Publishing Group;* 2012.

171. Smith GB, Prytherch DR, Meredith P, Schmidt PE, Featherstone PI. The ability of the National Early Warning Score (NEWS) to discriminate patients at risk of early cardiac arrest, unanticipated intensive care unit admission, and death. *Resuscitation*. 2013;84(4):465-70.
172. Candel BG, Dap S, Raven W, et al. Sex differences in clinical presentation and risk stratification in the Emergency Department: An observational multicenter cohort study. *Eur J Intern Med*. 2022;95:74-9.
173. Raisi-Estabragh Z, Kobo O, Elbadawi A, et al. Differential Patterns and Outcomes of 20.6 Million Cardiovascular Emergency Department Encounters for Men and Women in the United States. *Journal of the American Heart Association*. 2022:e026432.
174. Harrell FE. *Regression modeling strategies: with applications to linear models, logistic and ordinal regression, and survival analysis*: Springer; 2015.
175. Moons KG, Harrell FE, Steyerberg EW. Should scoring rules be based on odds ratios or regression coefficients? *J Clin Epidemiol*. 2002;55(10):1054-5.
176. Steyerberg EW, Vickers AJ, Cook NR, et al. Assessing the performance of prediction models: a framework for some traditional and novel measures. *Epidemiology (Cambridge, Mass)*. 2010;21(1):128.
177. Panday RN, Minderhoud T, Alam N, Nanayakkara P. Prognostic value of early warning scores in the emergency department (ED) and acute medical unit (AMU): A narrative review. *Eur J Intern Med*. 2017;45:20-31.
178. Steyerberg EW. *Clinical prediction models*: Springer; 2019.
179. Vergouwe Y, Royston P, Moons KG, Altman DG. Development and validation of a prediction model with missing predictor data: a practical approach. *J Clin Epidemiol*. 2010;63(2):205-14.
180. Tarassenko L, Clifton DA, Pinsky MR, Hravnak MT, Woods JR, Watkinson PJ. Centile-based early warning scores derived from statistical distributions of vital signs. *Resuscitation*. 2011;82(8):1013-8.
181. Watkinson PJ, Pimentel MAF, Clifton DA, Tarassenko L. Manual centile-based early warning scores derived from statistical distributions of observational vital-sign data. *Resuscitation*. 2018;129:55-60.
182. Bingisser R, Baerlocher SM, Kuster T, Nieves Ortega R, Nickel CH. Physicians' disease severity ratings are non-inferior to the emergency severity index. *Journal of Clinical Medicine*. 2020;9(3):762.
183. Brabrand M, Hallas J, Knudsen T. Nurses and physicians in a medical admission unit can accurately predict mortality of acutely admitted patients: a prospective cohort study. *PLoS One*. 2014;9(7):e101739.
184. Eckart A, Hauser SI, Kutz A, et al. Combination of the National Early Warning Score (NEWS) and inflammatory biomarkers for early risk stratification in emergency department patients: results of a multinational, observational study. *BMJ open*. 2019;9(1):e024636.
185. Elliott A, Taub N, Banerjee J, et al. Does the Clinical Frailty Scale at triage predict outcomes from emergency care for older people? *Ann Emerg Med*. 2021;77(6):620-7.
186. Gilbert T, Neuburger J, Kraindler J, et al. Development and validation of a Hospital Frailty Risk Score focusing on older people in acute care settings using electronic hospital records: an observational study. *The Lancet*. 2018;391(10132):1775-82.
187. Elliott A, Phelps K, Regen E, Conroy SP. Identifying frailty in the Emergency Department—Feasibility study. *Age Ageing*. 2017;46(5):840-5.

188. Candel BG, Raven W, Lameijer H, et al. The effect of treatment and clinical course during Emergency Department stay on severity scoring and predicted mortality risk in Intensive Care patients. *Critical Care*. 2022;26(1):1-9.
189. Riley RD, Ensor J, Snell KI, et al. External validation of clinical prediction models using big datasets from e-health records or IPD meta-analysis: opportunities and challenges. *BMJ*. 2016;353.
190. Steyerberg EW, Nieboer D, Debray TP, van Houwelingen HC. Assessment of heterogeneity in an individual participant data meta-analysis of prediction models: an overview and illustration. *Stat Med*. 2019;38(22):4290-309.
191. Madley-Dowd P, Hughes R, Tilling K, Heron J. The proportion of missing data should not be used to guide decisions on multiple imputation. *J Clin Epidemiol*. 2019;110:63-73.
192. Churpek MM, Yuen TC, Edelson DP. Predicting clinical deterioration in the hospital: the impact of outcome selection. *Resuscitation*. 2013;84(5):564-8.
193. Pimentel MA, Redfern OC, Gerry S, et al. A comparison of the ability of the National Early Warning Score and the National Early Warning Score 2 to identify patients at risk of in-hospital mortality: a multi-centre database study. *Resuscitation*. 2019;134:147-56.
194. Azur MJ, Stuart EA, Frangakis C, Leaf PJ. Multiple imputation by chained equations: what is it and how does it work? *Int J Methods Psychiatr Res*. 2011;20(1):40-9.
195. Steyerberg EW, Bleeker SE, Moll HA, Grobbee DE, Moons KG. Internal and external validation of predictive models: a simulation study of bias and precision in small samples. *J Clin Epidemiol*. 2003;56(5):441-7.
196. Bouch DC, Thompson JP. Severity scoring systems in the critically ill. Continuing education in anaesthesia, critical care & pain. 2008;8(5):181-5.
197. van de Klundert N, Holman R, Dongelmans DA, de Keizer NF. Data resource profile: the Dutch National Intensive Care Evaluation (NICE) registry of admissions to adult intensive care units. *Int J Epidemiol*. 2015;44(6):1850-h.
198. Arts D, de Keizer N, Scheffer G-J, de Jonge E. Quality of data collected for severity of illness scores in the Dutch National Intensive Care Evaluation (NICE) registry. *Intensive Care Med*. 2002;28(5):656-9.
199. Koetsier A, Peek N, De Keizer N. Identifying types and causes of errors in mortality data in a clinical registry using multiple information systems. *Quality of Life through Quality of Information: IOS Press*; 2012. p. 771-5.
200. Zeserson E, Goodgame B, Hess JD, et al. Correlation of venous blood gas and pulse oximetry with arterial blood gas in the undifferentiated critically ill patient. *J Intensive Care Med*. 2018;33(3):176-81.
201. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med*. 2001;345(19):1368-77.
202. Pappachan JV, Millar B, Bennett ED, Smith GB. Comparison of outcome from intensive care admission after adjustment for case mix by the APACHE III prognostic system. *Chest*. 1999;115(3):802-10.
203. Gunnerson KJ, Bassin BS, Havey RA, et al. Association of an emergency department-based intensive care unit with survival and inpatient intensive care unit admissions. *JAMA network open*. 2019;2(7):e197584-e.
204. Harrell F. Regression coefficients and scoring rules. *J Clin Epidemiol*. 1996;49(7):819.

205. Grove WM, Meehl PE. Comparative efficiency of informal (subjective, impressionistic) and formal (mechanical, algorithmic) prediction procedures: The clinical–statistical controversy. *Psychol Public Policy Law*. 1996;2(2):293.
206. van der Vegt AE, Holman M, ter Maaten JC. The value of the clinical impression in recognizing and treating sepsis patients in the emergency department. *Eur J Emerg Med*. 2012;19(6):373-8.
207. Kahneman D, Klein G. Conditions for intuitive expertise: a failure to disagree. *Am Psychol*. 2009;64(6):515.
208. Kahneman D, Tversky A. Subjective probability: A judgment of representativeness. *Cogn Psychol*. 1972;3(3):430-54.
209. Tversky A, Kahneman D. Availability: A heuristic for judging frequency and probability. *Cogn Psychol*. 1973;5(2):207-32.
210. Einhorn HJ, Hogarth RM. Confidence in judgment: Persistence of the illusion of validity. *Psychol Rev*. 1978;85(5):395.
211. Bushyhead JB, Christensen-Szalanski JJ. Feedback and the illusion of validity in a medical clinic. *Med Decis Making*. 1981;1(2):115-22.
212. Inghammar M, Sundén-Cullberg J. Prognostic significance of body temperature in the emergency department vs the ICU in Patients with severe sepsis or septic shock: A nationwide cohort study. *PLoS One*. 2020;15(12):e0243990.
213. Shimazui T, Nakada T-a, Walley KR, et al. Significance of body temperature in elderly patients with sepsis. *Critical Care*. 2020;24(1):1-9.
214. de Gelder J, Lucke JA, Blomaard L, et al. Optimization of the APOP screener to predict functional decline or mortality in older emergency department patients: cross-validation in four prospective cohorts. *Exp Gerontol*. 2018;110:253-9.
215. Blomaard LC, Lucke JA, Gelder Jd, et al. The APOP screener and clinical outcomes in older hospitalized internal medicine patients. *Neth J Med*. 2020;78(1):25-33.
216. Wynants L, Van Calster B, Collins GS, et al. Prediction models for diagnosis and prognosis of covid-19: systematic review and critical appraisal. *BMJ*. 2020;369.
217. Sheller MJ, Edwards B, Reina GA, et al. Federated learning in medicine: facilitating multi-institutional collaborations without sharing patient data. *Sci Rep*. 2020;10(1):1-12.

LIST OF PUBLICATIONS

This thesis

Candel, B. G., Dap, S., Raven, W., Lameijer, H., Gaakeer, M. I., de Jonge, E., & de Groot, B. (2022). Sex differences in clinical presentation and risk stratification in the Emergency Department: An observational multicenter cohort study. *European Journal of Internal Medicine*, 95, 74-79.

Candel, B. G., Duijzer, R., Gaakeer, M. I., Ter Avest, E., Sir, Ö., Lameijer, H., ... & de Groot, B. (2022). The association between vital signs and clinical outcomes in emergency department patients of different age categories. *Emergency Medicine Journal*, 39(12), 903-911.

Candel, B. G., Khoudja, J., Gaakeer, M. I., Ter Avest, E., Lameijer, H., Hessels, R. A., ... & de Groot, B. (2022). Age-adjusted interpretation of biomarkers of renal function and homeostasis, inflammation, and circulation in Emergency Department patients. *Scientific reports*, 12(1), 1-9.

Nissen, S. K., **Candel, B. G.**, Nickel, C. H., de Jonge, E., Ryg, J., Bogh, S. B., ... & Brabrand, M. (2022). The Impact of Age on Predictive Performance of National Early Warning Score at Arrival to Emergency Departments: Development and External Validation. *Annals of Emergency Medicine*, 79(4), 354-363.

Candel, B. G., van Ingen, I. B., van Doormalen, I. P., Raven, W., Mignot-Evers, L. A., de Jonge, E., & de Groot, B. (2022). The difference between the patients' initial and previously measured systolic blood pressure as predictor of mortality in older emergency department patients. *European Geriatric Medicine*, 13(2), 359-365.

Candel, B. G., Raven, W., Lameijer, H., Thijssen, W. A., Temorshuizen, F., Boerma, C., ... & de Groot, B. (2022). The effect of treatment and clinical course during Emergency Department stay on severity scoring and predicted mortality risk in Intensive Care patients. *Critical Care*, 26(1), 1-9.

Candel, B. G., Nissen, S. K., Nickel, C. H., Raven, W., Thijssen, W., Gaakeer, M. I., ... & de Groot, B. (2023). Development and External Validation of the International Early Warning Score for Improved Age-and Sex-Adjusted In-Hospital Mortality Prediction in the Emergency Department. *Critical Care Medicine*, 51(7), 881-891.

Candel, B. G., Raven, W., Nissen, S. K., Morsink, M. E., Gaakeer, M. I., Brabrand, M., ... & de Groot, B. (2023). The association between systolic blood pressure and heart rate in Emergency Department Patients: A multicenter cohort study. *The Journal of Emergency Medicine*.

Other publications

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Candel, B. G., Vaes, S. M., van Bree, E. M., Groenen, S. M., Derkx, F., Mignot, L. A., & de Groot, B. (2021). Telemedicine in the emergency department to decrease personal protective equipment use: a before-and-after study. *Emergency Medicine Journal*, 38(3), 224-228.

Candel, B. G., Karsonopoero, C. A., Arpots, R., Mans, S., Morsink, M. E., & Duijst, W. L. (2022). Nauwelijks bezwaar van SEH-patiënten tegen terugkoppeling medische gegevens. *Nederlands Tijdschrift voor Geneeskunde*, 166-D6384.

Candel, B. G., & Nissen, S. K. (2023). Use TRIPOD when validating clinical prediction models. *Emergency Medicine Journal*, 40(1), 81-81.

Candel, B. G., de Groot, B., Nissen, S. K., Thijssen, W. A., Lameijer, H., & Kellett, J. (2022). The prediction of 24-h mortality by the respiratory rate and oxygenation index compared with National Early Warning Score in emergency department patients: an observational study. *European Journal of Emergency Medicine*, 10-1097.

Kellett, J., Holland, M., & **Candel, B. G.** (2023). Using Vital Signs to Place Acutely Ill Patients Quickly and Easily into Clinically Helpful Pathophysiologic Categories: Derivation and Validation of Eight Pathophysiologic Categories in Two Distinct Patient Populations of Acutely Ill Patients. *The Journal of Emergency Medicine*, 64(2), 136-144.

CURRICULUM VITAE

Bart Gerard Jan Candel was born on the 29th of November 1990 in Oosterhout, the Netherlands. After graduating from secondary school at the Frencken College in Oosterhout he studied medicine at the University of Maastricht. He took a gap year between his bachelor's and master's and was living for half a year in Cape Town following an internship in trauma surgery at the Tygerberg Hospital in 2011. Bart was an active member of the athletics association UROS, triathlon association Ferro Mosae, and student association KoKo in Maastricht.

After his studies, he started to gain interest in acute care and worked as a resident in Emergency Medicine and Intensive Care Medicine at the Máxima Medical Center in Veldhoven, Catharina Hospital in Eindhoven, dr. Horacio Oduber Hospital in Aruba, and the Elisabeth-Tweesteden hospital in Tilburg. Formal training in Emergency Medicine started in 2019 under the supervision of Mieke van Campen-Hoekstra, followed by Fenneke van de Wiel. During his residency, Bart started doing research in the field of Emergency Medicine. Around 2020 he started his Ph.D. under the supervision of Dr. Bas de Groot and Prof. Dr. Evert de Jonge at the Leiden University Medical Center, studying age and sex adjusted risk stratification in the acute care, which has resulted in this thesis. Since 2022 he is an Emergency Physician and he has worked at the Emergency Department of the St. John of God Midland Hospital, and Fiona Stanley Hospital in Perth. Bart will continue doing research in the field of Emergency Medicine.

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