Cognitive impairment in older emergency department patients

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Jacinta Anna Lucke

The studies described in this thesis were performed at the department of Emergency Medicine of the Leiden University Medical Center, Leiden; HMC Bronovo Hospital, the Hague; Alrijne Hospital, Leiderdorp and Erasmus Medical Center, Rotterdam, the Netherlands.

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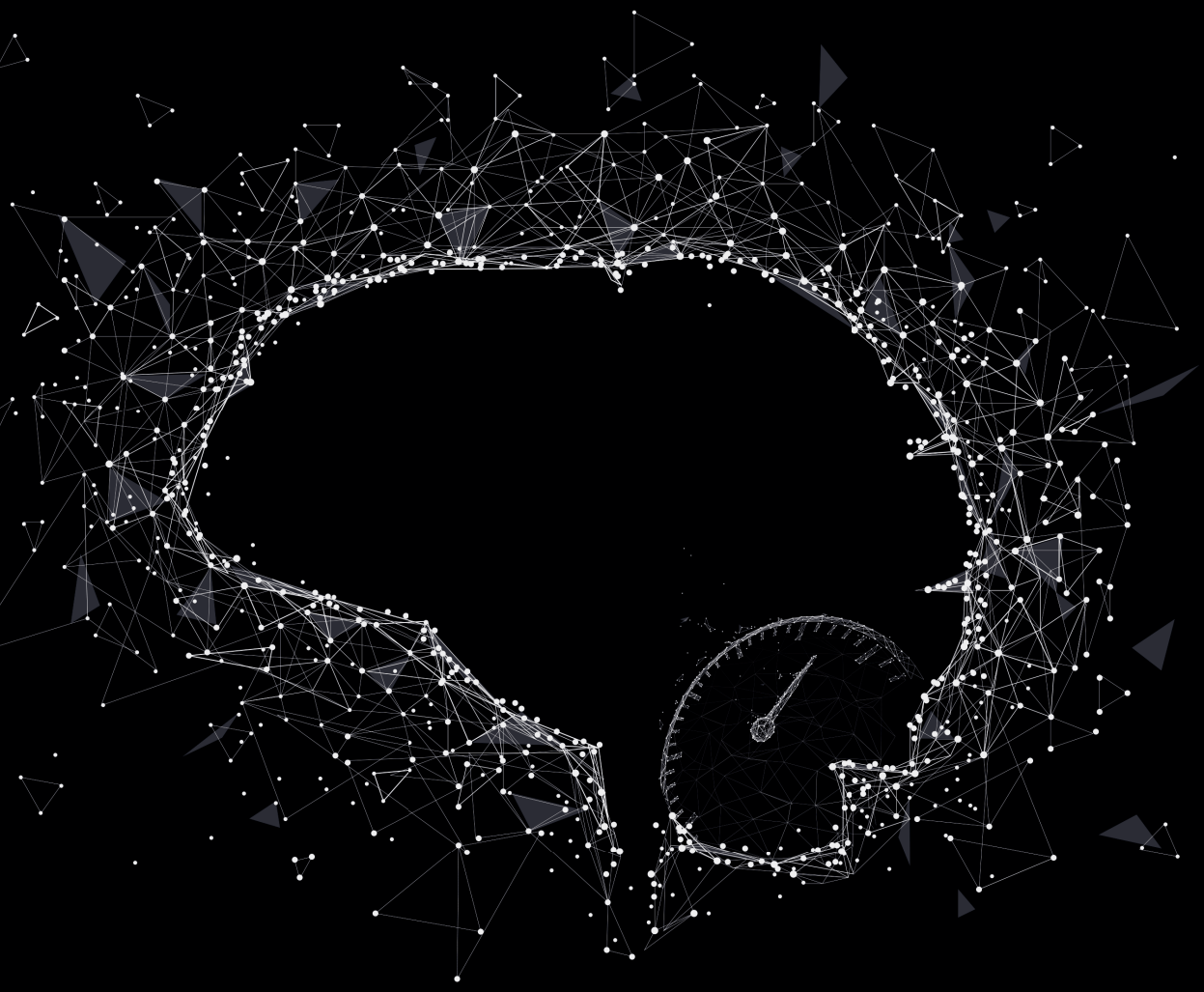

Chapter 1

Introduction

INTRODUCTION

General introduction

Older patients in the Emergency Department

With the ageing population increasing numbers of people aged 70-years and older are admitted at the Emergency Department (ED)[1]. The number of patients who visit the ED because of a fall has risen with approximately 2% per year[2] and the number of older patients who die because of a fall has increased with 60% in the last five years, with the majority of the victims being 80-years or older[3]. While the percentage of people aged 70-years and older in the Dutch population is 13%[4], they account for 24% of ED visits[5]. Because of the complexity of their medical and social problems, older patients remain longer admitted at the ED[6], attributing to the problem of ED crowding[7], which is in itself a risk factor for negative health outcomes[6, 8]. One of the main issues contributing to this problem is cognitive impairment of the older patient.

Cognitive impairment

Cognitive impairment is one of the most important issues in older ED patients, with a prevalence of approximately 20-40% in different health care systems[9, 10]. In the Emergency Department cognitive impairment *per se* is frequently missed[11]. Also, delirium is frequently missed, which may be caused by the existence of comorbid neuropsychiatric disorders, prominent pain, illness or hypoactive presentation[12, 13]. The clinical heterogeneity of the delirium syndrome and varying skills of assessors also contributes to the lack of identification of delirium in the ED. Cognitive impairment is known to be associated with adverse outcomes such as ED revisits, decline in quality of life and functional decline[14-16] from several studies in subsets of patients. Several screening instruments for use in the ED have been proposed, such as the 4AT and 6-Item Cognitive Impairment Test (6-CIT)[17], but none have been implemented on a wide scale. There are various systemic, neurological and psychiatric causes of cognitive impairment, such as dementia, delirium, brain hypoperfusion, stroke, and brain tumours. But irrespective of the cause, cognitive disorders have several important practical consequences, amongst others for history taking, treatment decisions and the explanation of treatment plans. It seems therefore important to determine the cognitive status of an ED patient as soon as possible to optimize the diagnostic and treatment processes, and the care during the ED stay. However so far, the association between cognitive impairment and adverse outcomes has not been extensively studied in large cohorts of unselected older ED patients.

Prediction of adverse outcome

Designing care models to provide optimal care for older patients has been an important research topic in the last decade, however, the perfect model has not been found yet due to the complexity of the issue. Comprehensive geriatric assessment and a multidisciplinary specialist care team approach is sometimes seen as the gold standard of care[18], but is not always feasible due to limited time, financial means and resources[19]. Several screening tools exist to assess the risk of adverse outcomes in older ED patients. The purpose of such tools is to identify older patients with the highest risk in order to implement protective measures for these patients specifically. However, available tools that use solely 'geriatric factors' like the Identification of Seniors at Risk (ISAR)[20], and Triage Risk Screening Tool (TRST)[21] are not accurate enough to discriminate high from low risk groups[22]. Also tests that exclusively look at cognitive impairment (i.e. the Mini Mental State Examination (MMSE[23])) cannot discriminate properly, complicating the development of cost-effective and well targeted interventions. Prediction models can behave differently in different patient populations, which requires attention during the derivation, validation and implementation of new screening instruments[24]. The range of the predictor values in a different population, the incidence of the predictors in the population, the face validity and the availability of better alternative models determines whether a model can be used in clinical practice. The purpose of the Acutely Presenting Older Patient (APOP) study was therefore to first identify easily collected parameters, with high prevalence and discriminatory properties, associated with adverse outcomes. After which we aimed to design a prediction model with a high positive predictive value as a first step towards improving care for older patients in the ED, taking into account cognitive impairment as a major determinant.

Aim of thesis

The primary aim of this thesis was to investigate whether cognitive impairment is associated with adverse outcomes in older patients acutely presenting to the ED. The second aim was to assess whether routinely collected parameters in addition to cognitive impairment can be used to screen for high risk of adverse outcome in older ED patients. The third aim was to investigate whether a proportion of older ED patients might have cognitive impairment due to impaired brain perfusion and oxygenation. These aims are a first step towards the design of screening instruments and implementation of interventions to improve the care for older patients in the ED.

Outline of thesis

This thesis is divided into two parts.

In the first part, the association between cognitive impairment and adverse outcomes in acutely presenting older patients is investigated in two different settings. In **chapter**

2 we studied whether acutely hospitalised older patients with impaired cognition, as measured using the 6-CIT, have a higher chance of 90-day functional decline and mortality, as well as prolonged hospital length of stay, admission to a nursing home and in-hospital mortality. **Chapter 3** studies whether impaired cognition is independently associated with 90-day and one year functional decline and mortality in older ED patients.

The second part of this thesis consists of five studies about the development of prediction models and screening instruments to identify patients with a high risk of adverse events.

In **chapter 4** we investigate whether routinely collected parameters at arrival of older patients in the ED can predict 90-day mortality. **Chapter 5** studies the prediction of hospital admission using routinely collected parameters at arrival to the ED and compares the predictive capabilities of these models between younger and older patients. In **chapter 6** we combine the knowledge drawn from previous chapters and study the refinement of the APOP-screener to identify patients with high risk of functional decline and mortality. In **chapter 7** delirium incidence in the ED is measured using two different delirium screeners. Finally, we explore future perspectives for research in cognitively impaired older patients. We hypothesize that a proportion of patients might have cognitive impairment due to impaired brain perfusion and oxygenation. Therefore, in **chapter 8** we investigate if vital signs, as a measure of acute hemodynamic changes, associate with cognitive impairment in older ED patients.

In **chapter 9** a general summary and discussion, with points for future research are provided.

Overview of used patient cohorts

Herstelzorg cohort

The Herstelzorg cohort is the result of a prospective multi-centre study 'Recovery Care Programme' (*Herstelzorgprogramma*)[25]. This was an observational study in which data were prospectively collected during three consecutive years in three secondary care facilities and one tertiary care hospital in the Netherlands which included acutely hospitalised patients aged 70-years and older. Cognition was assessed using the 6-CIT. Available endpoints were 90-day mortality, in-hospital mortality, admission to a nursing home and hospital length of stay.

APOP retrospective cohort

The Acutely Presenting Older Patient (APOP) retrospective cohort is a retrospective cohort, including all patients aged 18 years and older who visited the ED of the Leiden University Medical Center (LUMC) during the year 2012. Available parameters in this

cohort consisted of demographic data (age and sex), triage category, mode or arrival to the ED, type of medical specialist, whether laboratory tests were performed and vital signs. The endpoint of hospital admission was available in all patients. Mortality data was only available in patients aged 70-years and older.

APOP prospective cohort

The Acutely Presenting Older Patient (APOP) prospective cohort is an observational, multicentre study which took place in two secondary care and two tertiary care hospitals in the Netherlands. Patients were included between September 2014 and January 2017. Patients aged 70-years and older were included in this study. Within 1 hour of arrival to the ED a battery of tests was performed by trained medical students, among which were the 6-CIT score, CAM-ICU and Katz-ADL. Other available parameters were demographic characteristics, mode of arrival to the ED, triage category, vital signs, laboratory test results and geriatric characteristics. Endpoints were three months and one year functional decline and mortality.

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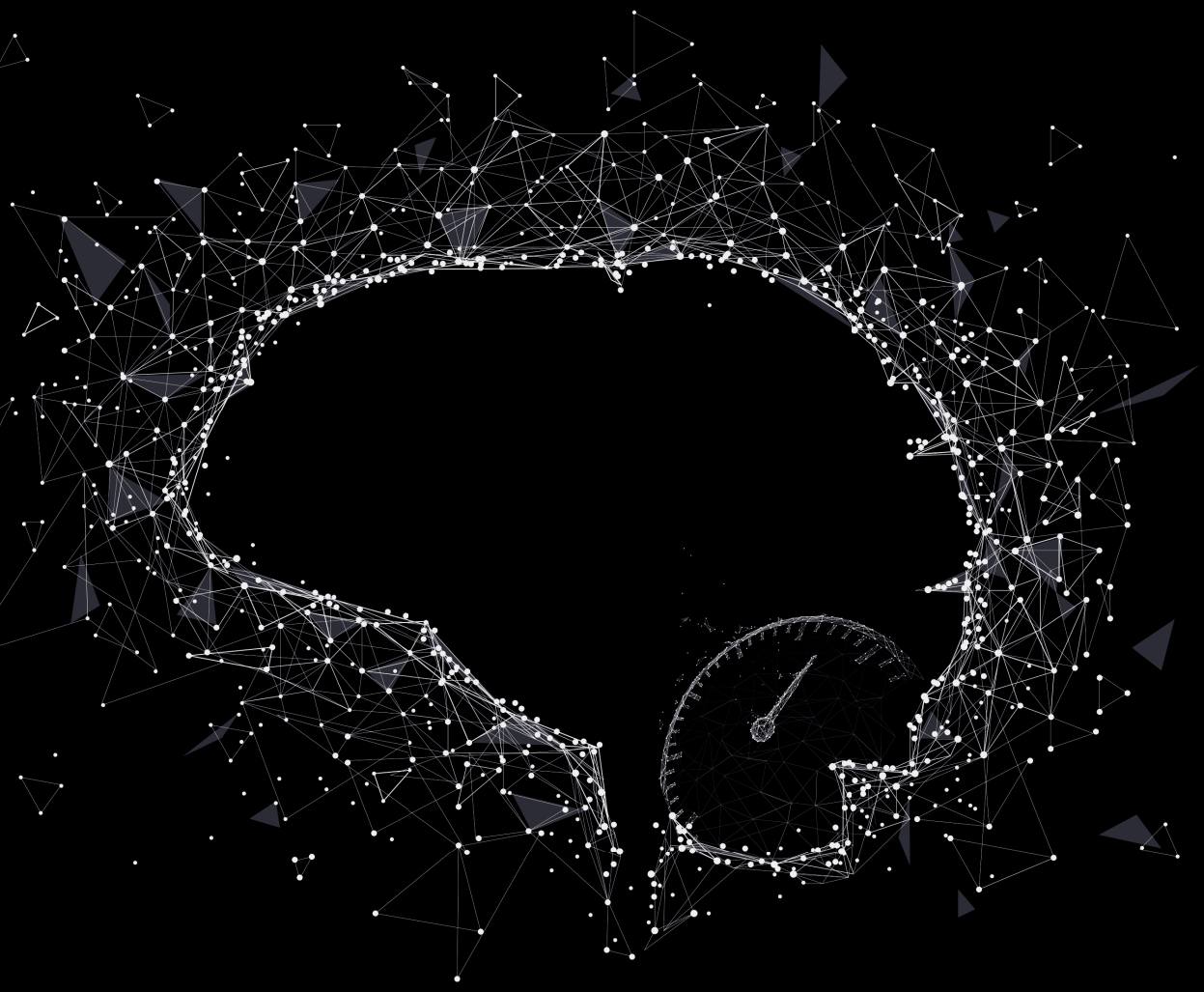
Part I

Cognitive impairment and adverse outcomes



Chapter 2

Cognitive impaired older patients and adverse outcomes after acute hospitalisation

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The Six-Item Cognitive Impairment Test (6-CIT) is associated with adverse outcomes in acutely hospitalised older patients; a prospective cohort study

ABSTRACT

Introduction: Cognitive impairment in older patients is a risk factor for functional decline and mortality. The aim of the present study was to investigate whether cognitive impairment, whichever the cause and measured by the Six-Item Cognitive Impairment Test (6-CIT), is an independent predictor of adverse outcomes in acutely hospitalised older patients.

Methods: For this secondary analysis of a prospective multicentre study, all acutely hospitalised patients aged 70-years and older were included during similar 4-month periods in 3 consecutive years. Multivariable logistic regression analyses were used to investigate whether impaired cognition (6-CIT ≥11 points) was an independent predictor of 90-day (long-term) adverse outcome, a composite measure of functional decline and 90-day mortality. Secondary (short-term) endpoints were hospital length of stay, new institutionalisation and in-hospital mortality.

Results: In total, 196 (15.6%) of 1252 included patients had a 6-CIT ≥11. Median age was 80 years (interquartile range 74-85). Patients with impaired cognition as assessed with the 6-CIT had a higher rate of 90-day adverse outcome (41.7% compared to 30.3% in 1056 not cognitively impaired patients, p=0.009). Impaired cognition was a predictor of 90-day adverse outcome with a crude odds ratio (OR) of 1.64 (95%CI 1.13-2.39), but statistical significance was lost when fully corrected for age, sex, living situation and specialism (OR 1.44, 95%CI 0.98-2.11). For all secondary outcomes (hospital length of stay, new institutionalisation and in-hospital mortality) impaired cognition was an independent predictor.

Conclusion: Acutely hospitalised older patients are frequently cognitively impaired. In the acute hospital setting the 6-CIT, a brief and easy to administer test for assessment of cognitive impairment, is associated with 90-day mortality and functional decline and is an independent predictor of hospital length of stay, new institutionalisation and in-hospital mortality. This emphasizes the importance of routinely screening for cognitive impairment in this vulnerable patient group.

INTRODUCTION

Acute hospitalised older patients have a high risk of adverse outcomes[1] and cognitively impaired older patients are at an even greater risk compared to patients with normal cognition[2]. Cognitive impairment can be caused by dementia, delirium, hypoperfusion of the brain or by a combination of these disorders. Impaired cognition is highly prevalent in acutely hospitalised older patients, but is frequently missed by doctors and nurses. Whichever the cause, professional caretakers should be vigilant for the presence of cognitive impairment as it calls for measures to prevent adverse events and to ensure safety when patients are hospitalised.

To date, in most studies investigating predictors of outcome among hospitalised older patients, the Mini Mental State Examination (MMSE)[3] was used to assess cognitive impairment, often in combination with pre-morbid ADL dependency[4-7]. However, a cognition test to be used in the acute hospital setting should be short, easy to administer and feasible when patients are unable to write. While the MMSE is considered the gold standard test, it has limitations due to the relatively lengthy time it takes to administer, its interaction with the level of education and the requirement to be able to write. In comparison with the MMSE, the Six-Item Cognitive Impairment Test (6-CIT) [8] takes only 2-3 minutes[9], is not influenced by educational level, can be used in bedbound patients who are unable to write and showed comparable test characteristics. If adverse outcome of acutely hospitalised older patients could be predicted by impaired cognition as assessed with the 6-CIT, it would be a suitable test to improve identification of older patients at risk for adverse events in the acute setting and to help identify their needs.

Therefore, the aim of the present study was to investigate the association of impaired cognition, as measured with the 6-CIT, and adverse outcomes in acutely hospitalised older patients. A cohort study among three hospitals in the Netherlands was conducted and a distinction was made in short-term adverse outcomes (in-hospital mortality, new institutionalisation and prolonged length of hospital stay) and long-term adverse outcomes (90-day functional decline and mortality).

METHODS

Study design and setting

This was a secondary analysis using the data of a prospective multicentre study the 'Recovery Care Programme' (*HerstelZorgProgramma*)[10]. A detailed description of the study design can be found in the article by Heim *et al.*[10]. In summary, this was an observational cohort study in which data were prospectively collected during 3 consecu-

tive years, in the same season. Three secondary care facilities (Alrijne Hospital, Leiden; Alrijne Hospital, Leiderdorp and HMC Bronovo Hospital, The Hague) and one tertiary care hospital (Leiden University Medical Center, Leiden) participated.
The medical ethics committee of the Leiden University Medical Center (LUMC) waived the need for ethical approval as data was collected to improve patient care. All patients provided written informed consent and data was treated anonymously.

Participants

Patients aged 70-years or older who were admitted to one of the four study hospitals were assessed for inclusion. Two secondary care hospitals and one tertiary care hospital included both acutely admitted and planned patients (wards of orthopaedics, neurology, urology and surgery). One secondary care hospital included only acutely admitted patients. For the analyses the wards of orthopaedics, urology and surgery were combined into 'surgery', and the departments of internal medicine, neurology and cardiology were combined into 'medical'.
Patients were excluded if they stayed in the hospital for less than 48 hours and if they were not able to perform the study interview within 72 hours after admission. Patients who had an MMSE of less than 19, indicating severe cognitive impairment, and had no caregiver present during the interview were also excluded because they could not provide informed consent. For the present secondary analysis only acutely admitted patients, from both medical and surgical departments, were included.

Data collection

Patients were interviewed on the wards by a trained nurse with a series of questionnaires. After 90-days, patients were sent follow-up questionnaires by mail, to be self-administered. Patients who did not respond were contacted by telephone.

Cognitive function

The Six-Item Cognitive Impairment Test (6-CIT)[8] contains items on orientation, attention and memory with a range from 0-28; a score ≥11 indicates cognitive impairment. The 6-CIT showed a good correlation with the MMSE and a cut-off point of eleven corresponded to a MMSE of ≤23[9]. The 6-CIT score was used to classify older people in those with (score ≥11) and without (score <11) cognitive impairment, a cut-off as has been recommended in literature.
Mini Mental State Examination (MMSE) evaluates overall cognitive functions, such as orientation, memory, attention, calculation[3], ranging from 0-30, and a score ≤23 indicating cognitive impairment. Scores <19 indicate severe cognitive impairment.

Functional status

The Katz Index of Independence in Activities of Daily Living[11] (Katz-ADL) was administered to quantify functional status. The Katz-ADL contains six yes/no items on whether a patient is independent in bathing, dressing, transferring from bed to chair, eating, going to the toilet and the use of incontinence products. A score ≥ 2 points means dependency in ADL[12].

Demographics

Data on age, sex and self-reported living situation were registered by the research nurse. Also the medical specialism and hospital were the patient was treated was registered.

Outcomes

Primary outcome

The primary outcome was defined as a composite end-point of adverse outcome, containing self-reported functional decline (by increasing one point in Katz-ADL) after 90-days and/or mortality within 90-days. Mortality was verified in the hospital files, by the healthcare insurer or was reported by family members. The cut-off point of ≥1 point increase in Katz-ADL was chosen because this results in a clinically relevant decrease in independency[12].

Secondary outcomes

Three secondary outcomes were investigated: in-hospital mortality, new institutionalisation directly after hospital admission and prolonged hospital length of stay (LOS). New institutionalisation was defined as moving from an independent living situation to assisted home care facilities directly after discharge from the hospital. Prolonged hospital LOS was defined as a length of stay of 7 days or longer.

Data analysis

Data are displayed as percentages, means and standard deviations for normally distributed variables or as medians with interquartile range for non-normally distributed variables. Independent T-tests and chi-square tests were used to assess equality of groups when variables were normally distributed and with Mann-Whitney-U tests for non-normally distributed variables. The association between 6-CIT and primary and secondary outcomes was calculated using crosstabs and chi-square tests. Patients were divided into two groups for analysis, using the 6-CIT (≤10, ≥11) at baseline. Univariable logistic regression was used to assess the crude association between 6-CIT and primary and secondary outcomes.

Two multivariable logistic regression models were used to assess whether 6-CIT was an independent predictor of adverse outcome. The first model was corrected for age

and sex. In the second model the association of interest was also corrected for living situation and specialism, to correct for baseline functional status and type of disease. The general rule of thumb that there should be a minimum of 10 events per possible variable in the model was used.

Statistical significance was defined by 95% confidence intervals excluding 1.0 or $p<0.05$. All statistical analyses were performed using IBM SPSS Statistics package (version 23, New York, USA).

RESULTS

Baseline characteristics

A total of 1252 patients was included in this study (figure 1), of which the baseline characteristics are shown in table 1. The majority of patients was female (n=710, 56.8%) and median age was 80 years (interquartile range 74-85). In 196 patients (15.6%), the 6-CIT score was ≥11, indicating cognitive impairment. In table 1, it is shown that patients with cognitive impairment were older, less frequently male and more often lived in an assisted living facility, compared to patients with a lower 6-CIT score.

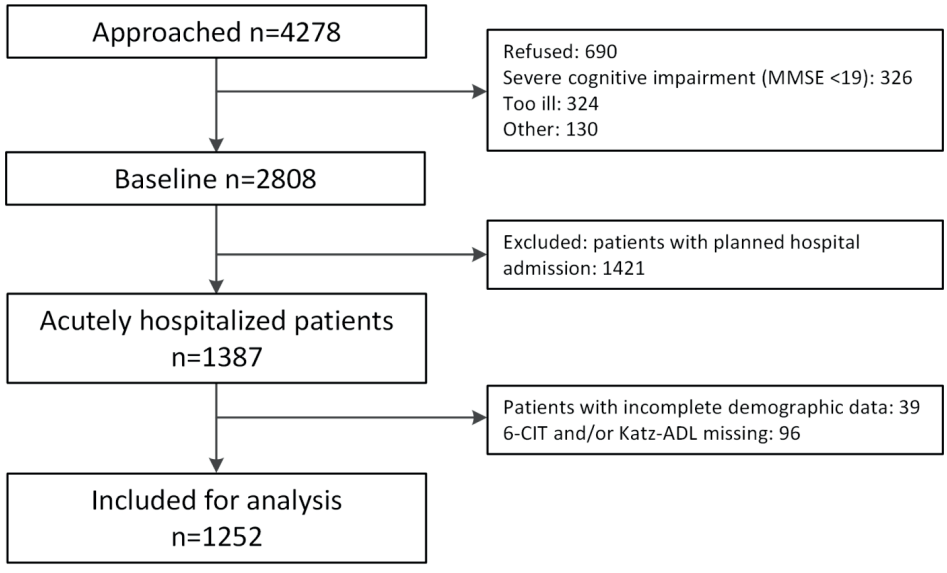

Figure 1: Flowchart of study population

Table 1: Baseline characteristics of the total study population, and stratified according to 6-CIT score

Characteristic	All patients n=1252	6-CIT ≤10 n=1056	6-CIT ≥11 n=196	p-value
Age	80 (74-85)	79 (74-84)	82 (78-87)	<0.001
Male n,%	542 (43.2)	476 (45.1)	66 (33.7)	0.003
Living situation[a] n,%				<0.001
Independent, with others	591 (47.5)	519 (49.4)	72 (36.9)	
Independent, alone	522 (41.9)	443 (42.2)	79 (40.5)	
Assisted living facility	132 (10.6)	88 (8.4)	44 (22.6)	
Specialism[b] n,%				0.740
Surgical	770 (61.7)	647 (61.5)	123 (62.8)	
Medical	478 (38.3)	405 (38.5)	73 (37.2)	
Hospital n,%				<0.001
LUMC	205 (16.4)	166 (15.7)	39 (19.9)	
Alrijne - Leiden	297 (23.7)	240 (22.7)	57 (29.1)	
Alrijne - Leiderdorp	375 (30.0)	308 (29.2)	67 (34.2)	
HMC Bronovo	375 (30.0)	342 (32.4)	33 (16.8)	
Katz-ADL[c]	1 (0-3)	0 (0-2)	1 (0-4)	<0.001
6-CIT	4 (0-8)	2 (0-5)	14 (12-18)	n.a
MMSE[d]	27 (24.3-29)	28 (26-29)	21 (19-24)	n.a.

Data are presented as median with interquartile range unless noted otherwise.
Abbreviations; n: number, 6-CIT: Six-Item Cognitive Impairment Test, Katz-ADL: Katz Index of Independence in Activities of Daily Living, IQR: interquartile range, n.a.: not applicable.
[a]number of values 1245; [b]number of values 1248; [c]number of values 1252; [d]number of values 892.

Primary and secondary outcomes

A total of 311 (31.8%) patients suffered from 90-day mortality or functional decline. Table 2 shows the incidence of various negative outcomes over strata of 6-CIT. More than 30% of patients with a 6-CIT ≤10 suffered from 90-days mortality or functional decline, in comparison to 41.7% patients with 6-CIT ≥11 (p=0.009). Patients with impaired cognition had a prolonged hospital stay of ≥7 days more frequently (n=455, 43.3% vs. n=108, 55.4%, respectively p=0.002) and were more often institutionalised after hospital admission, compared to those with a normal cognition. Also, in-hospital mortality was higher in cognitively impaired patients compared to cognitively normal patients (n=12, 1.2% vs. n=8, 4.1%, respectively p=0.003).

Table 2: Crude outcomes for total study population and according to 6-CIT-score

	Total n=1252	6-CIT ≤10 n=1056	6-CIT ≥11 n=196	p-value
Primary outcome				
90-day adverse outcome[a]	311 (31.8)	256 (30.3)	55 (41.7)	0.009
Secondary outcomes				
≥7 days LOS[b]	563 (45.1)	455 (43.3)	108 (55.4)	0.002
New institutionalisation[c]	67 (7.4)	46 (5.8)	21 (18.8)	<0.001
In-hospital mortality[d]	20 (1.6)	12 (1.2)	8 (4.1)	0.003

Data are presented as numbers and percentages.
Abbreviations: n: number, 6-CIT: Six-Item Cognitive Impairment Test, IQR: interquartile range, LOS: length of stay.
[a]number of values 977; [b]number of values 1247; [c]number of values 905; [d]number of values 1236.

Independent predictors

Patients with impaired cognition as assessed with the 6-CIT had a 1.6 times increased risk of mortality or functional decline after 90-days (OR 1.64, 95%CI 1.13-2.39). When corrected for age and sex this association was still observed but after correction for living situation and treating medical specialism, statistical significance was lost (table 3). Patients with impaired cognition were also at increased risk of prolonged hospital stay and of an 3-fold increased risk of being institutionalised, independent of age, sex, living situation, medical specialism. Finally, impaired cognition was independently associated with in-hospital mortality.

Table 3: The association between 6-CIT and adverse outcomes in older acutely hospitalised patients

	6-CIT ≤10	6-CIT ≥11	p-value
		OR (95%CI)	
Primary outcome – 90 day functional decline and mortality[a]			
Crude	1 (ref)	1.64 (1.13-2.39)	0.010
Model 1 – corrected for age and sex	1 (ref)	1.48 (1.01-2.17)	0.045
Model 2 - age, sex, living situation and specialism	1 (ref)	1.44 (0.98-2.11)	0.066
Secondary outcome - ≥7 days LOS[b]			
Crude	1 (ref)	1.63 (1.20-2.22)	0.002
Model 1 – corrected for age and sex	1 (ref)	1.51 (1.11-2.07)	0.009
Model 2 - age, sex, living situation and specialism	1 (ref)	1.54 (1.12-2.12)	0.008
Secondary outcome - New institutionalisation[c]			
Crude	1 (ref)	3.74 (2.14-6.56)	<0.001
Model 1 – corrected for age and sex	1 (ref)	2.94 (1.64-5.28)	<0.001
Model 2 - age, sex, living situation and specialism	1 (ref)	3.45 (1.89-6.31)	<0.001

Table 3: The association between 6-CIT and adverse outcomes in older acutely hospitalised patients (*continued*)

	6-CIT ≤10	6-CIT ≥11	p-value
		OR (95%CI)	
Secondary outcome – in-hospital mortality[d]			
Crude	1 (ref)	3.67 (1.48-9.10)	0.005
Model 1 – corrected for age and sex	1 (ref)	3.18 (1.26-8.05)	0.015
Model 2 - age, sex, living situation and specialism	1 (ref)	3.11 (1.21-7.99)	0.018

Abbreviations: OR=Odds Ratio, 95%CI= 95% Confidence Interval, 6-CIT= Six-Item Cognitive Impairment Test

[a]Patients included for analysis 977; [b]Patients included for analysis 1247; [c]Patients included for analysis 905; [d]Patients included for analysis 1236.

DISCUSSION

The present study shows that, in acutely hospitalised older patients with impaired cognition, as defined by a 6-CIT score ≥11, there is an association with increased risk 90-day adverse outcome (functional decline and mortality). We interpret the fact that statistical significance was lost after adjustment as a result of adding more variables in the model, as the estimate remained virtually unchanged. Further it is shown that impaired cognition is independently associated with a hospital LOS ≥7 days as well as increased in-hospital mortality and institutionalisation.

Our findings are in line with the literature, reporting an association between impaired cognition and functional decline, mortality and hospital length of stay[2, 6, 13-15]. Care providers often experience barriers in administering a cognition test in the acute setting. If such a test would be used on a regular basis, nurses and doctors could take instant tailor-made actions e.g. history taking, explaining treatment, involving relatives at an early stage and taking measures to prevent or treat delirium, which might prevent adverse outcomes in older patients. Several screening tools for measuring cognitive dysfunction have been proposed[14, 16]. The 6-CIT appears to be an instrument that can be easy and quickly applied, has a low chance of interpretation error and can also be administered in patients who are unable to read, write or perform lengthy tests[10, 16]. In this study, we further showed that the 6-CIT is an independent predictor of adverse outcomes, such as prolonged hospitalisation, institutionalisation and in-hospital mortality. Because of this combination of test characteristics and association with adverse outcomes, it might be a good tool to implement in daily practice.

In our study we used the 6-CIT for screening of cognitive impairment, irrespective of its cause, and showed that patients who are cognitively impaired have an increased risk of adverse outcomes. Dementia and delirium are the main causes of cognitive impairment

in older patients, but they can be difficult to diagnose and differentiate in the acute setting. As been recently proposed by Jackson *et al.*[17], cognitive impairment *per se* in acute hospital admissions is common and associated with poor health outcomes. Therefore, when managing acutely ill older patients, it is important to treat them based on their needs, rather than on a specific diagnosis. Therefore, medical staff needs to be vigilant and assess cognition on a routine basis. A short test such as the 6-CIT could facilitate this. In case of impaired cognition, the patient should be treated optimally in terms of optimizing the care process, providing environmental adjustments and minimizing harms[17]. The pro-active diagnosis of impaired cognition *per se*, whatever the specific underlying diagnosis, is likely to improve patient experience and outcomes, because the caregiver can focus on interventions, rather than on diagnostics. Furthermore, cognitive impairment should be considered when developing health care policies for improvement of outcomes such as hospital length of stay, new institutionalisation and in-hospital mortality.

We did not find an independent association of cognitive impairment and long term outcome, probably because adding more variables to the model borderline significance was lost. However, the estimates remained virtually unchanged.

The present study has several limitations. First, the exclusion of patients with a MMSE <19 points leads to an underestimation of the prevalence of cognitive impairment. However, in patients with more subtle cognitive impairment, the 6-CIT adds possibly unknown clinical information, while severely cognitive impaired patients are recognized relatively easily (e.g. nursing home patients with known dementia). Secondly, the 22% loss to follow-up after 90-days may have led to selection bias. However, the patients who were lost to follow-up were likely more cognitively impaired and frail, which leads to an underestimation of the association found in this study.

Major strengths of this study are the large sample size and multicentre design. Also, the duration of the study, in 3 consecutive years, during similar months renders the study more robust as temporary environmental effects are less likely to have influenced the data. The combination of both long and short term outcomes is another strength of this study.

In conclusion, cognitive impairment measured with the 6-CIT associates with 90-day adverse outcomes in acutely admitted older patients and is an independent predictor of prolonged hospital length of stay, institutionalisation and in-hospital mortality. This emphasizes the importance of routinely screening for cognitive impairment in this vulnerable patient group. Further research should focus on integrating cognition in risk-screening tools and investigate whether interventions for patients with impaired cognition improves clinically relevant outcomes.

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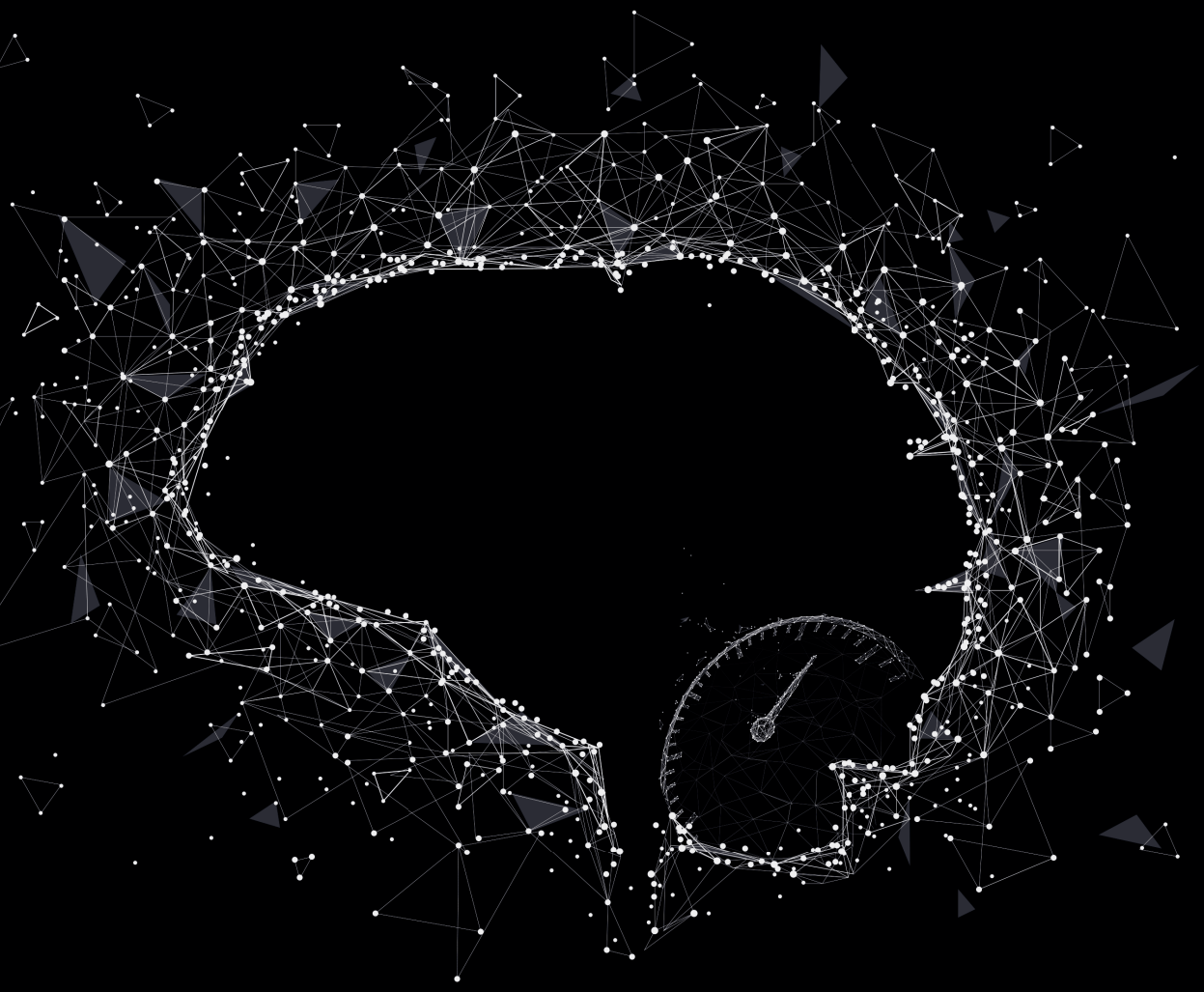

Chapter 3

Cognitive impaired older patients and adverse outcomes after a visit to the ED

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Impaired cognition is associated with adverse outcome in older patients in the ED; the APOP-study

ABSTRACT

Objective: To investigate whether cognitive impairment, measured early after Emergency Department arrival and irrespective of its cause, is independently associated with functional decline or mortality after 3 and 12 months in older Emergency Department patients.

Design and setting: A prospective multicentre cohort study in all Acutely Presenting Older Patients visiting the Emergency Department (APOP-study) of three hospitals in the Netherlands.

Participants: 2130 patients, ≥70-years.

Measurements: Data on demographics, disease severity and geriatric characteristics were collected during the first hour of the Emergency Department visit. Cognition was measured using the Six-Item Cognitive Impairment Test (6-CIT). Cognitive impairment was defined as 6-CIT ≥11, self-reported dementia or the inability to perform the cognition test. The composite adverse outcome after 3 and 12 months was defined as a 1-point decrease in Katz Index of Independence in Activities of Daily Living (Katz-ADL) new institutionalisation or mortality. Multivariable regression analysis was used to assess whether cognitive impairment independently associates with adverse outcome.

Results: Of 2130 included patients, 588 (27.6%) had cognitive impairment at baseline and 654 patients (30.7%) suffered from adverse outcome after three months. Cognitive impairment associated with increased risk for adverse outcome (adjusted odds ratio (OR) 1.72, 95%CI 1.37-2.17). After twelve months, 787 patients (36.9%) suffered from adverse outcome. Again, cognitive impairment independently associated with increased risk for adverse outcome (adjusted OR 1.89, 95%CI 1.46-2.46). Odds ratios were similar for patients who were discharged home versus hospitalised patients.

Conclusion: Cognitive impairment measured during the early stages of Emergency Department visit, irrespective of the cause, is independently associated with adverse outcome after three and twelve months in older patients.

INTRODUCTION

The prevalence of impaired cognition in older Emergency Department (ED) patients ranges from 20 to 40%[1, 2]. Irrespective of its cause, impaired cognition is an important indicator that a patient has a vulnerable brain and may suffer from other comorbidities or previously unrecognized frailty[3] and may be at risk for developing delirium. However, impaired cognition is frequently underdiagnosed in the ED[4].

Impaired cognition can have numerous causes, either transient or pre-existing, such as dementia, delirium and circulatory failure as a result of severe disease causing hypo perfusion of the brain. Cognitive impaired patients have a higher chance of adverse outcome, such as functional decline[5], decreased quality of life[6], moving to a nursing home after being hospitalised[7] and revisits to the ED[8]. Emphasis in research in the ED has been on diagnosing delirium, for which multiple screeners exist[9, 10]. However, these screening tools are specific for delirium, for instance because they score the acute onset or fluctuation of symptoms, or inattention, which may not be present in a patient with pre-existing cognitive impairment. Arguably, also these patients may benefit from early recognition, for instance by implementing delirium prevention measures prior to the delirium occurring or because of communication needs of the cognitively impaired older patient. It is, however, unclear impaired cognition measured shortly (<1 hour) after the start of the ED visit, associates with adverse outcomes.

The goal of this investigation is to assess whether there is an independent association between impaired cognition, measured early during the ED visit, and functional decline or mortality after three and twelve months in older ED patients. We performed a large prospective, multicentre study in the Netherlands.

METHODS

Study design and setting

A detailed description of the of the Acutely Presenting Older Patient (APOP) study was previously published[11]. In short, during 3 consecutive months all patients aged 70-years and older visiting the Emergency Department were included in this multicentre prospective cohort study. One tertiary care hospital (Leiden University Medical Center) and two secondary care hospital (Alrijne Hospital and HMC Bronovo Hospital) participated.

Selection of participants

All patients were included consecutively. Inclusion criteria were age 70-years and older. Patients who were triaged for a need of immediate care (Manchester Triage category Red), patients with an unstable medical condition, due to denied permission of the

nurse or physician to enter the room and patients with a disturbed mental status without a proxy to provide informed consent were excluded. Also patients with a language barrier were not eligible. Please see Appendix 1 in the supplementary data on the journal website (http://www.ageing.oxfordjournals.org) for more information about the selection of participants. Written informed consent was obtained before inclusion from all participants. The medical ethics committee of the LUMC, Alrijne Hospital and HMC Bronovo Hospital approved the study.

Methods and measurements

For extended methods and measurements please see Appendix 1 in the supplementary data on the journal website (http://www.ageing.oxfordjournals.org/). Cognition was measured using the Six-Item Cognitive Impairment test (6-CIT)[12]. Patients were stratified for analyses: those with a 6-CIT ≤10 were considered to have normal cognition, 6-CIT ≥11 was considered cognitive impairment[13]. Also patients with self-reported dementia, or those unable to perform the 6-CIT were categorized as 'impaired cognition'.

Outcome

The main outcome of the study was composite adverse outcome, a composite of functional decline or mortality at three months follow up. Functional decline was defined as at least one point increase in Katz-ADL score or new institutionalisation, defined as moving to a nursing- or residential care home within three months after ED visit. Three months after the ED visit the patient was contacted by telephone. In case of no response after three attempts in three consecutive days, the general practitioner (GP) was contacted to verify phone number and living status and a letter was sent. Data concerning mortality was derived from the municipal records at three months follow-up. If a patient did not decease within three months but no data on functional status was available, the patient was considered to have no composite adverse outcome. A similar endpoint was available at twelve months.

Analysis

Baseline characteristics are presented as mean with standard deviation (SD) in case of normal distribution, median with interquartile range (IQR) in case of skewed distribution or as numbers with percentages (%). Using univariable and multivariable regression analysis with endpoint 'cognitive impairment' the independent predictors of cognitive impairment in older ED patients were assessed. Chi-square test was used to assess crude associations between cognitive impairment and functional decline or mortality. Univariable and multivariable logistic regression was used to assess the association between cognition and functional decline or mortality after three months. Please see Appendix 1 for a more detailed description of used models and sensitivity analysis.

The level of significance was set at P<0.05. Statistical analyses were performed using IBM SPSS Statistics package (version 23).

Declaration of sources of funding

This work was supported by the Netherlands Organisation for Health Research and Development (grant number 627004001). The sponsor had no role in the design of the study, methods, study recruitment, collection or analysis of the data and had no role in the preparation of the paper.

RESULTS

A total of 2130 patients participated in this study, which is a 83.4% inclusion rate of all eligible patients (please see the figure Appendix 2 in the supplementary data on the journal website http://www.ageing.oxfordjournals.org/).

Baseline characteristics

Table 1 shows the baseline characteristics of the study population. Of all included patients 588 (27.6%) had cognitive impairment according to a 6-CIT score ≥11, of which 122 (5.7% of the total cohort) reported to be diagnosed with dementia (supplemental table S1). Compared to patients with normal cognition, patients with cognitive impairment were older (median 83 years vs median 78 years), less frequently high educated (13.2% vs 25.3%) and more often living in residential care or nursing home (20.7% vs 4.5%). Cognitively impaired patients arrived by ambulance more frequently (66.2% vs 45.7%), suffered from more urgent problems (triage urgency <1 hour, 62.1 vs 54.6%), more often had a fall related visit (35.2% vs 24.3%), had more impairment on the other geriatric characteristics tests because they used a walking device more frequently (63.0% vs 36.1%), had a higher Katz-ADL score (median 1 vs median 0) and had more hours of home-care (median 2.5 vs median 0). Please see Appendix 3 for a baseline characteristics of patients, stratified by cognition status.

Characteristics of impaired cognition

Appendix 4 shows which predictors independently associated with the risk of having impaired cognition. Demographic characteristics like higher age and higher level of education, triage urgency, fall related ED visit and main complaint 'malaise', 'dyspnoea' or 'psychiatric complaint' were independent predictors of having impaired cognition. Finally, a higher Katz-ADL at baseline was independently associated with risk of having impaired cognition.

Table 1: Baseline characteristics of acutely presenting older patients, stratified by cognition status

Characteristics	All patients n=2130	Normal cognition[a] n=1542	Impaired cognition[b] n=588	p-value between groups
Demographics				
Age (years), median (IQR)	79 (74-85)	78 (74-83)	83 (77-88)	<0.001
Male	953 (44.7)	691 (44.8)	262 (44.7)	0.916
High education	466 (22.0)	389 (25.3)	77 (13.2)	<0.001
Living in a residential care/nursing home	191 (9.0)	69 (4.5)	122 (20.7)	<0.001
Hospital				0.185
LUMC	751 (35.3)	561 (36.4)	190 (32.3)	
Alrijne	881 (41.4)	631 (40.9)	250 (42.5)	
HMC Bronovo	498 (23.4)	350 (22.7)	148 (25.2)	
ED presentation characteristics				
Arrival by ambulance	1093 (51.3)	704 (45.7)	389 (66.2)	<0.001
Triage urgency				<0.001
> 1 hour	616 (28.9)	488 (31.7)	128 (21.8)	
< 1 hour	1207 (56.7)	842 (54.6)	365 (62.1)	
< 10 minutes	306 (14.4)	211 (13.7)	95 (16.2)	
Blood tests performed	1696 (79.6)	1216 (78.9)	480 (81.6)	0.155
Fall related ED visit	582 (27.3)	375 (24.3)	207 (35.2)	<0.001
Main complaint				<0.001
Minor trauma	669 (31.6)	475 (31.0)	194 (33.2)	
Malaise	398 (18.8)	260 (17.0)	138 (23.6)	
Chest pain	334 (15.8)	292 (19.1)	42 (7.2)	
Abdominal pain	214 (10.0)	167 (10.9)	47 (8.0)	
Dyspnea	240 (11.8)	157 (10.3)	93 (15.9)	
Other	112 (5.3)	88 (5.8)	24 (4.1)	
Syncope	101 (4.8)	72 (4.7)	29 (5.0)	
Major trauma	16 (0.8)	12 (0.8)	4 (0.7)	
Psychiatric complaint	21 (1.0)	7 (0.5)	14 (2.4)	
Geriatric characteristics				
Hours of home-care, median (IQR)	0 (0-3)	0 (0-3)	2.5 (0-7)	<0.001
Use of walking device	923 (43.5)	555 (36.1)	386 (63.0)	<0.001
Number of medications, median (IQR)	5 (3-8)	5 (3-7)	5 (3-8)	1.00
Katz-ADL, median (IQR)[c]	0 (0-1)	0 (0-1)	1 (0-3)	<0.001
6-CIT score, median (IQR)[d]	4 (2-9)	3 (0-6)	16 (13-21)	-

Data are presented as number, percentage unless noted otherwise.
Abbreviations: n=number, IQR=interquartile range, ED=Emergency Department, 6-CIT=6 Item Cognitive-Impairment-Test, Katz-ADL: Katz Index of Independence in Activities of Daily Living.
Missing values: use of walking device (n=8), level of education (n=10), triage category (n=1), main complaint (n=15), Katz-ADL (n=31), hours of home care (n=63), number of medications (n=1), and 6-CIT score (n=202).
[a]6-CITscore 0-10, [b]6-CIT ≥11, dementia or missing cognition. [c]Higher scores indicate higher dependency (range 0-6), [d]Higher scores indicate more cognitive impairment, cut-off ≥11.

Association between impaired cognition and functional decline or mortality

In total 654 (30.7%) patients suffered from functional decline or mortality after three months. Older patients with impaired cognition had an increased risk (odds ratio (OR) 2.81, 95%CI 2.30-3.43) for functional decline or mortality after three months (table 2, figure 1). After adjustment for age, sex and education and additionally for disease severity, comorbidities and baseline functional status patients with impaired cognition had increased risk of functional decline or mortality (OR 1.72, 95%CI 1.37-2.17).

Table 2 also shows the association between impaired cognition and functional decline or mortality after twelve months. A number of 787 patients (36.9%) suffered from functional decline or mortality after twelve months. The risk of functional decline or mortality in patients with impaired cognition after 12 months was 3-fold higher when compared to those with normal cognition (OR 3.13, 95%CI 2.57-3.81, fully corrected model OR 1.91, 95%CI 1.52-2.39).

Table 2: The association between cognition and functional decline or mortality after three months in older Emergency Department patients

	Normal cognition[a]	**Cognitive Impairment[b]**	**p-value**
	n=1542	**n=588**	
Three months functional decline or mortality, n (%)[c]	375 (24.3)	279 (47.4)	<0.001
		OR (95%CI)	
Crude	1 (ref)	2.81 (2.30-3.43)	<0.001
Model 1 – corrected for age, sex and education	1 (ref)	2.18 (1.76-2.70)	<0.001
Model 2 – corrected for age, sex, education, number of medications, ambulance arrival & triage	1 (ref)	1.99 (1.60-2.46)	<0.001
Model 3 - corrected for age, sex , education, number of medications, Katz-ADL, ambulance arrival & triage	1 (ref)	1.72 (1.37-2.17)	<0.001
Twelve months functional decline or mortality, n (%)[c]	454 (29.4)	333 (56.6)	<0.001
		OR (95%CI)	
Crude	1 (ref)	3.13 (2.57-3.81)	<0.001
Model 1 – corrected for age, sex and education	1 (ref)	2.37 (1.93-2.93)	<0.001
Model 2 – corrected for age, sex, education, number of medications, ambulance arrival & triage	1 (ref)	2.24 (1.81-2.78)	<0.001
Model 3 - age, sex , education, number of medications, Katz-ADL, corrected for ambulance arrival & triage	1 (ref)	1.91 (1.52-2.39)	<0.001

Abbreviations: n=number, OR=Odds Ratio, 95%CI= 95% Confidence Interval, Katz-ADL: Katz Index of Independence in Activities of Daily Living, 6-CIT= 6-Item Cognitive Impairment Test.
[a]6-CIT score 0-10, [b]6-CIT score 11-28, known dementia or missing 6-CIT [c]p-value calculated with chi-square test.

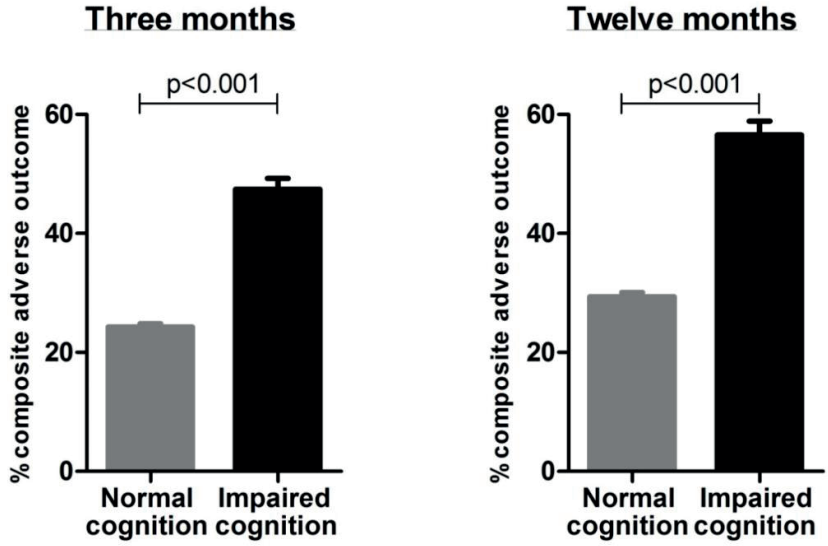

Figure 1: Incidence of functional decline or mortality for patients with normal and impaired cognition

Sensitivity analysis

We performed three sensitivity analyses. First, we studied the association between cognition and functional decline or mortality, using a lower cut-off point of ≥8 for the 6-CIT (Appendix 5). The total number of patients with impaired cognition in these analyses increased from 588 (27.6%) to 847 (39.7%). Impaired cognition was still independently associated, yet the associated risk was lower (OR 1.39, 95%CI 1.12-1.73). Predictors of impaired cognition and its association with functional decline or mortality were similar to the main analysis.

In a second sensitivity analysis, patients without dementia but in whom cognition could not be measured in the ED were excluded (Appendix 6). The results were comparable to the main analysis.

The third sensitivity analysis showed the association between cognitive impairment and functional decline or mortality, stratified for disposition (discharged home vs hospitalised, Appendix 7). Whereas the percentage of patients with cognitive impairment who suffered from functional decline or mortality after three months (38.2% vs 54.5%) was higher in the hospitalised patient group, the odds ratios for functional decline or mortality were very similar. Also, even when correcting for disease severity, comorbidity and Katz-ADL, the odds ratio for functional decline was similar for patients who were discharged home versus those who were hospitalised (OR 1.53, 95%CI 1.07-2.18 in discharged patients and OR 1.81, 95%CI 1.33-2.46 in hospitalised patients), indicating that cognitive impairment is evenly important to detect in patients discharged home from the ED. Please see the tables from Appendix 3-7 in the supplementary data on the journal website (http://www.ageing.oxfordjournals.org/).

DISCUSSION

Approximately a quarter of all older patients visiting the Emergency Department (ED) have impaired cognition. The main finding of this study is that cognitive impairment in older ED patients, irrespective of its cause, is associated with functional decline or mortality both after three months and twelve months, independent of demographic characteristics, disease severity, comorbidities and baseline functional status.

The results of a number of smaller studies in different populations and using different definitions of adverse outcome are in line with our finding that cognitive impairment is associated with functional decline or mortality. In one Canadian study including 1114 older ED patients with minor injuries, frailty and cognitively impaired older patients had an adjusted risk ratio for functional decline of 1.89 (95%CI 1.38-2.59) after three months[5]. This is comparable to our findings in our unselected patient group, although in our study cognition was measured within 30 minutes to 1 hour after ED arrival, while in the Canadian study cognition was assessed in the ED in 40% of the patients and within 7 days by telephone in approximately 60% of the patients. In another small study (n=188), patients with impaired cognition were admitted to a nursing home more often after hospitalisation, which is similar to our results. Finally, several studies investigated the association between cognitive impairment and other endpoints, like falls, hospital visits[14] and quality of life[6], and are therefore difficult to compare with the results of our study. Taken together, our study is the first to show the association of cognitive impairment with functional decline or mortality in unselected older ED patients.

We a priori hypothesized that cognitive impairment indicates increased vulnerability of the patients' brain that should be recognized because of the large implications. Our study shows that cognitive impairment *per se* is associated with functional decline or mortality when measured within one hour of ED arrival, irrespective of its cause, i.e. delirium, dementia, depression or hypoperfusion of the brain. Further, those with impaired cognition (e.g. dementia) and patients with hypoperfusion of the brain due to clinical illness are at increased risk of developing delirium. Finally, patients with pre-existing dementia can have superimposed delirium. Recognition of cognitive impairment *per se* may therefore may prevent delirium. Unfortunately, ED physicians frequently miss the presence of impaired cognition[4, 15-17], probably due to a lack of education, adequate screening tools and recognition of patterns associated with a diagnosis of impaired cognition. We showed in our study that the 6-CIT is associated with functional decline and mortality and may therefore be a sensible screening tool.

Besides the higher probability of delirium, cognitive impairment has other implications for ED management of older patients which may help in preventing the associated adverse outcomes. For example, cognitive impairment complicates understanding of discharge instructions and may result in worse outcomes. Written discharge instruc-

tion is therefore especially important in cognitive impaired older patients. In addition, older patients often have impairments in multiple geriatric domains, such as the social network and mobility issues. Cognitive impairment may further increases the risk of adverse events and calls for interventions.

In a recent essay by Jackson *et al.*[3] there is a strong call for treating older patients with cognitive impairment on a 'need of care' basis, rather than on the basis of a diagnosis. There is a need for joined up care between professionals to improve detection, diagnostics and management, whatever the specific underlying diagnosis. In this light, the current study emphasizes the importance of screening for cognitive impairment, shortly after arrival to the ED, because impaired cognition is associated with functional decline or mortality, irrespective of disease severity, comorbidities and geriatric factors. Currently, proper multi-domain screening tools for older ED patients are lacking[18] and when designing these, cognitive function, for example as measured by the 6-CIT should be taken into account.

This study has several limitations. First, cognition was tested within thirty minutes to one hour after arrival to the ED. This could have influenced the cognition score. A patient who is anxious or in pain may perform worse resulting in an overestimation of impaired cognition. Second, we did not perform a delirium screening test. We therefore have no information on whether impaired cognition was of 'acute onset' or not. However, we set out to study the association of cognitive impairment irrespective of the cause. A third limitation is the fact that 'known dementia' was a self-reported measurement and not confirmed by medical charts or by the general practitioner. Finally, we did not perform a cognition test at follow up, so we do not know whether the impaired cognition had persisted for several months, or was a temporary problem. However, these limitations did not influence the validity of the study.

The strengths of this study are the broad, unselected inclusion and the high inclusion rate. Another strength is the multicentre, prospective study design with a relatively large number of patients giving us the opportunity to draw conclusions about a broad patient group that made our results more generalisable. Third, the outcome measure is clinically relevant and collected with a low chance of bias. Mortality was checked with the municipality records and the Katz-ADL is a well-validated measure. Finally, this is the first large, multicentre study focussing on cognitive impairment and composite adverse outcome (functional decline and mortality) in unselected older ED patients.

To conclude, cognitive impairment is highly prevalent in older ED patients and is associated with functional decline or mortality, independent of the cause of cognitive impairment, baseline functional status, disease severity and comorbidities.

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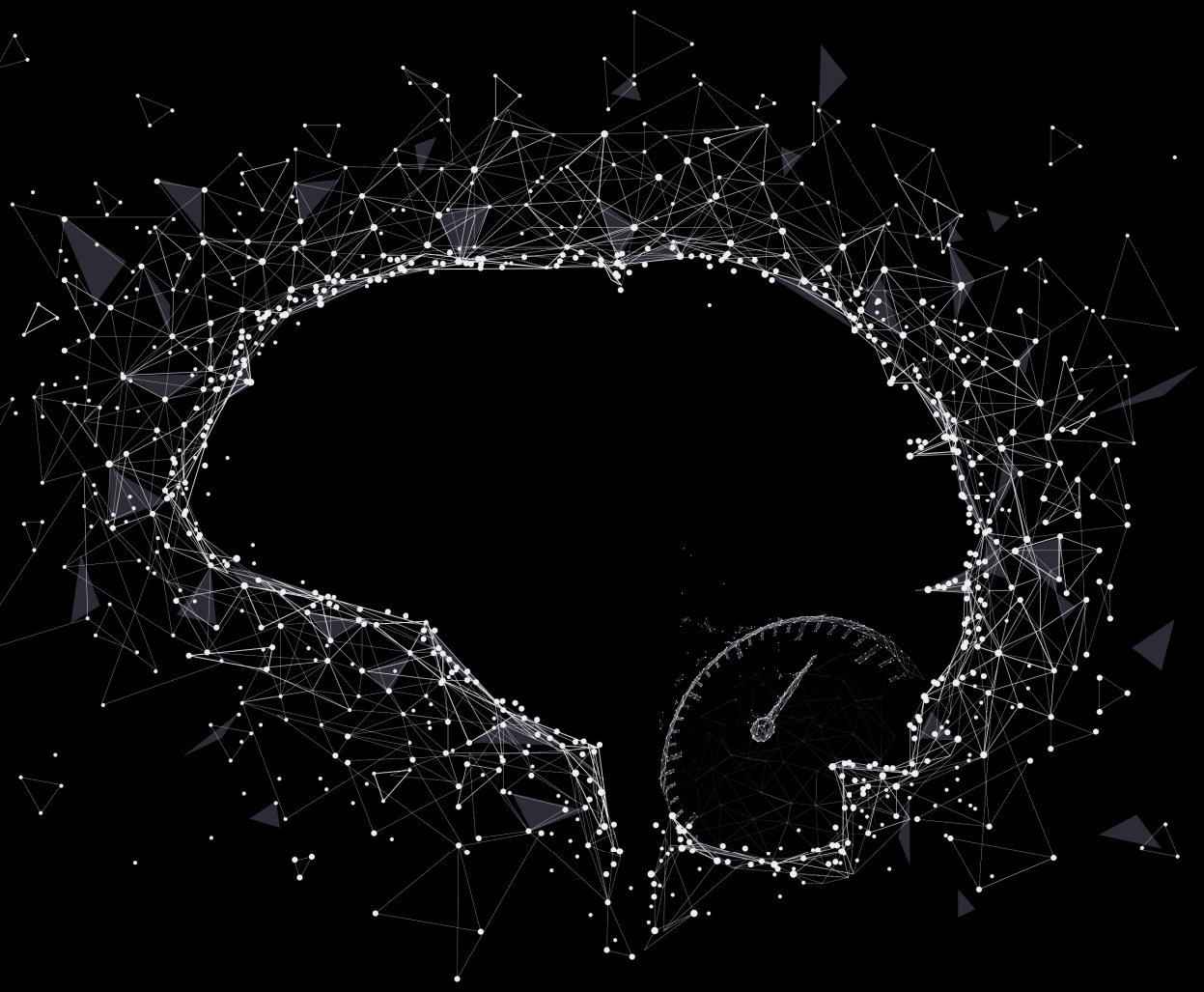
Part II

Screening for adverse outcomes in older Emergency Department patients



Chapter 4

Prediction of 90-day mortality in older ED patients

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Prediction of 90-day mortality in older patients after discharge from an Emergency Department: a retrospective follow-up study

ABSTRACT

Introduction: Older people frequently attend the Emergency Department (ED) and have a high risk of poor outcome as compared to their younger counterparts. Our aim was to study routinely collected clinical parameters as predictors of 90-day mortality in older patients attending our ED.

Methods: We conducted a retrospective follow-up study at the Leiden University Medical Center (The Netherlands) among patients aged 70-years or older attending the ED in 2012. Predictors were age, gender, time and way of arrival, presenting complaint, consulting medical specialty, vital signs, pain score and laboratory testing. Cox regression analyses were performed to analyse the association between these predictors and 90-day mortality.

Results: 3921 unique patients were eligible for inclusion. Ninety-day mortality was 10.5% for the total group. Independent predictors of mortality were age (hazard ratio [HR] 1.06, 95% confidence interval (95%CI) 1.04-1.08), referral from another hospital (HR 2.74, 95%CI 1.22-6.11), allocation to a non-surgical specialty (HR: 1.55, 95%CI 1.13-2.14), increased respiratory rate (HR up to 2.21, 95%CI 1.25-3.92), low oxygen saturation (HR up to 1.96, 95%CI 1.19-3.23), hypothermia (HR 2.27, 95%CI 1.28-4.01), fever (HR 0.43, 95%CI 0.24-0.75), high pain score (HR 1.55, 95%CI 1.03-2.32) and the indication to perform laboratory testing (HR 3.44, 95%CI 2.13-5.56).

Conclusion: Routinely collected parameters at the ED can predict 90-day mortality in older patients presenting to the ED. This study forms the first step towards creating a new and simple screening tool to predict and improve health outcome in acutely presenting older patients.

INTRODUCTION

Older patients frequently attend Emergency Departments (EDs) as compared to younger adults[1, 2]. Admittance to the ED is associated with risk of negative health outcomes such as functional decline[3] and mortality[2]. However, little is known about predictors of mortality in the period after presentation to the ED in older patients.

Predictors of poor outcome in older patients can be divided into two categories. On one hand, there is the level of vulnerability of the older patient, which is reflected in for instance multi-morbidity, polypharmacy, functional capacity and cognitive and social functioning[4]. Frequently studied prediction tools such as the Identification of Seniors At Risk[5] and the Triage Risk Screening Tool[6], are based on these parameters. On the other hand, parameters reflecting severity of disease at presentation may also determine poor outcome[7]. Specific diagnoses are well known predictors of mortality but are very numerous and hard to categorise, partly due to the large heterogeneity of older patients, especially in the presence of multi-morbidity[8]. Other, more generic data on severity of disease are routinely recorded as part of medical practice, e.g. time of arrival[9], vital signs[7] and laboratory parameters[10], and may also predict poor outcome. However, little is known about their association with mortality in older patients in the period after discharge from the ED. Identifying such predictors may enable us to design an adequate screening tool in order to target older patients at high risk of negative health outcome early during ED admittance. A screening tool may enable fast-tracking patients that are likely to be admitted to an inpatient ward and shorten their stay at the ED. In case of high risk of mortality advanced care planning may be initiated at the ED or shortly after admission, or rehabilitation in case of high risk of functional decline.

Our aim was to study whether routinely recorded parameters in the ED, such as way and time of arrival, vital signs and laboratory results independently predict 90-day mortality. We performed a retrospective follow-up study among patients aged 70-years or older visiting our ED.

METHODS

Study design

Our study was conducted at the ED of the Leiden University Medical Center, a tertiary university teaching and level 1 trauma hospital in the Netherlands. Patients aged 70-years and older that had attended the ED between 1 January 2012 and 31 December 2012 were included retrospectively. The Medical Ethics Committee of the Leiden University Medical Center waived the obligation of approval as data were collected in the past as part of routine clinical care.

Health care in the Netherlands

The Netherlands is a small and highly populated country in Europe measuring 41.5 thousand square kilometres[11] and counting 16.7 million people in 2012[12]. Standard medical care is equally accessible for every Dutch citizen through legally mandatory health insurance. Primary care is provided by General Practitioners (GPs). Specialist care can only be accessed after referral by a GP. One of the exceptions are EDs of hospitals, where a substantial proportion of patients are self-referred[13]. The Leiden University Medical Center is a tertiary referral centre in Leiden. The ED is one of two level 1 trauma EDs that together serve a catchment area of 400.000 inhabitants, both urban and rural. The population is predominantly Caucasian and includes all social classes. Our ED is equipped with 15 rooms of which 3 are specially designed to accommodate trauma victims. Patients are triaged by an ED nurse. Within hours self-referred patients are evaluated by an ED physician or ED resident. Out of hours self-referred patients are primarily evaluated by a GP and if indicated subsequently referred to an ED physician or ED resident. Referred patients are directly allocated to a resident of the appropriate medical specialty present at the ED. After evaluation, patients are either treated at the ED and discharged home or admitted to an inpatient ward. Patients with an electrocardiogram indicative for myocardial infarction bypass our ED and are immediately referred to the catheterisation laboratory[14]. As a consequence, they are not included in the present study.

Selection of study population

Patients were identified in our computerised patient record system (ChipSoft-EZIS®, version 5.2, 2006-2014, Amsterdam, The Netherlands, www.chipsoft.nl). Several steps of exclusion criteria were applied. Our study was aimed at a selection of older patients that may benefit from additional interventions during or following an ED visit. First, medical records based upon unjustified ED use were excluded. Unjustified ED use was defined as ED use for any other reason than acute medical care, such as outpatient check-ups on weekends, plaster cast readjustments, performed blood tests for other medical departments and patients who decided to leave the ED before medical attention was bestowed. We believe they are not representative for the acutely presenting older patient visiting the ED and may disturb associations between predictors and outcome results. Second, patients who deceased in the ED and patients receiving cardiopulmonary resuscitation therapy upon arrival were excluded from analysis since prognosis of these patients is known to be poor and these patients fall outside the scope for identifying new predictors[15]. As we used retrospective data, we were unable to assess whether an ED visit was the first or one of many visits. Patients may have visited other hospitals as well as ours or made visits outside our selected timeframe. Therefore, we included only the first ED visit of each patient in 2012.

Potential predictors

Apart from demographic characteristics (age and gender), we selected routinely collected parameters that may reflect severity of disease as presented in the acute situation. We investigated time and way of arrival, presenting complaint, consulting medical specialty, vital signs, pain score and laboratory parameters. These data were automatically generated from the digital patient records and outliers were manually checked for validity by a researcher. Triage category was not included since we were interested in universal predictors and hospitals differ in the triage systems they use.

Time of ED visit was determined from ED registration time and subdivided in three categories, day (08.00h-15.59h), evening (16.00h-23.59h) and night time (00.00h-07.59h). Way of arrival at the ED was mutually exclusively noted as self-referral, brought in by ambulance, referral by a GP, internal referral from another department or referral by another hospital. Patients categorised as self-referral or referral by a GP visited the ED with private transportation. By contrast, patients who arrived by ambulance were categorised as brought in by ambulance regardless of whether the ambulance was ordered by a referring GP or because of an emergency call. Dutch ambulance staff is trained to judge the accuracy of emergency calls at the scene. Ambulance staff will only transport such patients to the hospital if they consider the referral justified. At our hospital, triage is based on the Manchester Triage System (MTS)[16]. This system uses flow charts for 55 disease presentations to determine the level of urgency and associated target time a patient should receive care from a physician. The presenting complaints of our study population were categorised according to these MTS disease presentations[16]. Disease presentations occurring in less than 3% of patients were merged as 'other'. The medical specialty a patient was assigned to was categorised as surgical or non-surgical[17]. Finally, we listed clinical measurements that were recorded in the ED: vital signs, pain score and laboratory results. At triage, an ED nurse determined which clinical measurements were medically indicated according to protocols. They were measured at triage or soon after a patient was placed into a treatment room. Laboratory testing is performed on indication and either ordered by an ED nurse or consulting physician. The first set of vital signs assessed in the ED was recorded. Vital signs were categorised according to the Modified Early Warning Score and included systolic blood pressure, heart rate, respiratory rate and body temperature[18]. Oxygen saturation was recorded as well[19]. Categories containing less than 1% of patients were combined with adjacent categories, but not with the reference category, in order to minimise the number of categories. Pain was evaluated using the Numeric Rating Scale (NRS) rating from 0-10 and categorised as no or light (NRS 0-3), mild (NRS 4-6) and serious (7-10) pain according to the Dutch guidelines for pain classification in emergency settings[20]. Blood pressure, heart rate, respiratory rate and oxygen saturation were measured using a medical monitor (IntelliVue MP50®, Eindhoven, The Netherlands, www.philips.nl). Body temperature was de-

termined by a tympanic thermometer (Genius 2®, Mansfield, USA, www.covidien.com). Registered laboratory results were haemoglobin, thrombocytes, leukocytes, C-reactive protein, sodium, potassium, creatinine, urea, troponin T and non-fasted glucose. Vital signs and laboratory parameters will only be assessed if there is a medical indication to do so. If data on vital signs were missing, they were either not measured or they were measured but not recorded in the medical chart correctly. It is impossible to categorise this in a retrospective manner. Therefore, we assumed that missing vital signs meant that there was no indication to perform these measurements.

Outcome

Our primary outcome measure was mortality in the first three months after ED admittance. Beyond this time period, the association of predictors measured at baseline and mortality is likely to be obscured by the occurrence of new medical events. Mortality data were acquired from the municipal personal records database on 1 May 2014.

Statistical methods

Data are displayed as mean and standard deviation if normally distributed and median and interquartile range if not normally distributed. To investigate the association between predictors and mortality we used Cox proportional hazards models. We performed uni- and multivariable Cox regression analysis. In the univariable models only one parameter was entered as independent variable. In the multivariable analyses multiple parameters were entered as independent variables simultaneously to assess which were independent predictors of mortality. Our study was aimed at potential predictors assessed upon or soon after arrival at the ED. Results of laboratory testing became available at least one hour after withdrawal, but laboratory testing is usually ordered in the first few minutes after a patient is placed into a treatment room. Therefore, we added merely the medical indication to perform laboratory testing to the set of predictors in the multivariable model. As an in-depth analysis we additionally analyse the univariable association of individual laboratory results with mortality using univariable Cox regression. The level of significance was set at $p<0.05$. All statistical analyses were performed using IBM SPSS Statistics package (version 20).

RESULTS

During 2012, there were 27.862 Emergency Department (ED) visits of which 4458 (16%) visits were by patients aged 70-years or older. Visits were excluded because of inappropriate ED use (n=136), receiving cardiopulmonary resuscitation upon arrival (n=67) and

patients who deceased in the ED (n=5). This left 4250 suitable ED presentations of which 959 were repeat visits, leaving 3291 unique patients eligible for the analyses (figure 1).

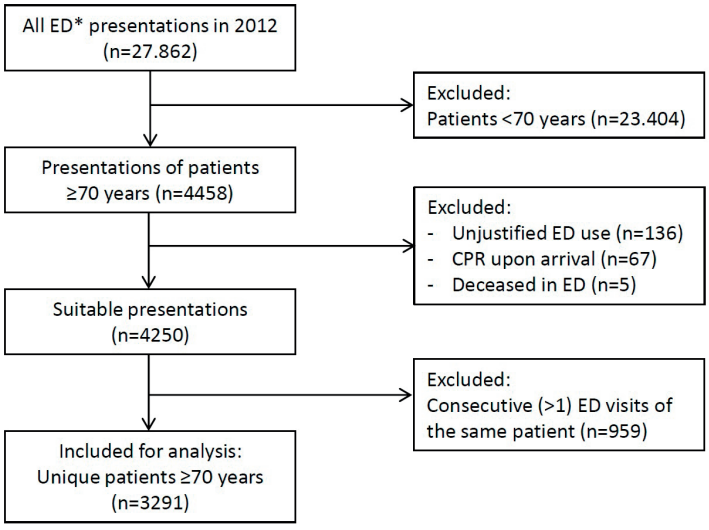

Figure 1: Flowchart of participant selection

Baseline characteristics of the study population are described in table 1. Median age was 78.3 years (interquartile range 74.0-83.6 years) and 53.1% was female. Most patients arrived by ambulance (35.2%) or with private transportation after referral by their GP (33.7%). Patients were assigned to a non-surgical specialty in 58.3% of cases. Mortality rate at 30 days after ED presentation was 7.0% and increased to 10.5% at 90 days after an ED visit (figure 2).

Regression analyses were performed to investigate the association between routinely assessed predictors in the ED and mortality in the first 90-days of follow-up (table 2). A substantial portion of the univariable associations remained significant in the multivariable model i.e., age (hazard ratio [HR] 1.06, 95% confidence interval [CI] 1.04-1.08), referral by another hospital (HR 2.74, 95%CI 1.22-6.11), presenting complaint classified as 'unwell' (HR 1.99, 95%CI 1.23-3.20), allocation to a non-surgical specialty (HR 1.55, 95%CI 1.13-2.14), increased respiratory rate 21-29/minute (HR 1.63, 95%CI 1.06-2.52; ≥30 /minute: HR 2.21, 95%CI 1.25-3.92), decreased oxygen saturation (91-94%: HR 1.63, 95%CI 1.16-2.31; ≤90%: HR 1.96, 95%CI 1.19-3.23), hypothermia (HR 2.27, 95%CI 1.28-4.01), fever (HR 0.43, 95%CI 0.24-0.75), high pain score (HR 1.55, 95%CI 1.03-2.32) and the indication to perform blood tests (HR 3.44, 95%CI 2.13-5.56).

Table 1: Baseline characteristics of study population

ED Characteristics	All unique patients[a] (n=3291)
Demographics	
Age, median (IQR)	78.3 (74.0-83.6)
Female	1748 (53.1)
Time of ED visit	
Day 08.00h-15.59h	1677 (51.0)
Evening 16.00h-23.59h	1254 (38.1)
Night 00.00h-07.59h	360 (10.9)
Way of arrival	
Self-referral	654 (19.9)
Brought in by ambulance	1159 (35.2)
General practitioner	1108 (33.7)
LUMC internal	338 (10.3)
Other hospital	28 (0.9)
Unknown	4 (0.1)
Presentation	
Limb problems	608 (18.5)
Unwell	598 (18.2)
Chest pain	346 (10.5)
Shortness of breath	304 (9.2)
Abdominal pain	214 (6.5)
Collapsed	168 (5.1)
Falls	122 (3.7)
Wounds	108 (3.3)
Palpitations	101 (3.1)
Other	722 (21.9)
Consulting medical specialty	
Surgical	1371 (41.7)
Non-surgical	1920 (58.3)
Vital signs	
Systolic BP, mmHg, mean (SD)	146.5 (28.3)
Heart rate/min, mean (SD)	83.7 (21.0)
Oxygen saturation, median (IQR)	98 (3)
Respiratory rate/min, mean (SD)	18.7 (5.5)
Temperature °C, mean (SD)	36.9 (1.0)
Pain score (NRS), median (IQR)	3 (1-5)
Laboratory results	
Haemoglobin (mmol/L), mean (SD)	8.1 (1.2)
Thrombocytes (*10^9/L), mean (SD)	229 (94)
Leukocytes (*10^9/L), median (IQR)	8.75 (6.80-11.41)
C-reactive protein (mg/L), median (IQR)	6.0 (0.0-30.0)
Sodium (mmol/L), mean (SD)	139 (4)
Potassium (mmol/L), mean (SD)	4.3 (0.6)

Table 1: Baseline characteristics of study population (*continued*)

ED Characteristics	All unique patients[a] (n=3291)
Creatinine (µmol/L), median (IQR)	84 (67-109)
Urea (mmol/L), median (IQR)	7.6 (5.9-10.2)
Troponin T (µg/L), median (IQR)	0.014 (0.007-0.028)
Non fasted glucose (mmol/L), mean (SD)	7.9 (3.3)

Data are presented as number, percentage unless noted otherwise.
Abbreviations: ED: emergency department, N: number, SD: standard deviation, IQR: interquartile range, h: hours, NRS: numeric rating scale.
Vital parameters measured are: 0_2: oxygen saturation, measured in percentage oxygenated haemoglobin. Systolic BP: Systolic blood pressure, measured in millimetres of mercury. Temperature measured in degrees Celsius. Heart rate and respiratory rate are measured as times per minute.
Missing data n,(%): systolic BP 768 (23.3), heart rate 719 (21.8), respiratory rate 1482 (45.0), temperature 1077 (32.7), pain score 173 (5.3), haemoglobin 831 (25.3), thrombocytes 1576 (47.9), leukocytes 831 (25.3), C-reactive protein 945 (28.7), sodium 873 (26.5), potassium 1021 (31.0), creatinine 873 (26.5), urea 878 (26.7), troponin T 1539 (46.8), glucose 908 (27.6).
[a] A unique patient was defined as the first presentation of a patient to our ED in 2012.

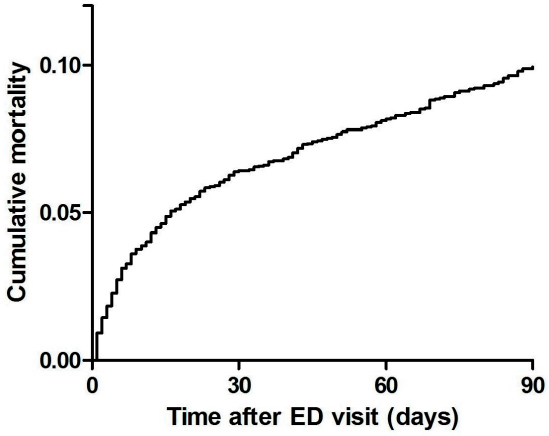

Figure 2: Cumulative mortality in older patients after an ED visit

Table 3 demonstrates how abnormal versus normal laboratory results relate to mortality risk among patients who had an indication for performing blood tests. The majority of abnormal laboratory results show an increased hazard as compared to measurements within normal range. Strongest associations were a high level of troponin T (HR 3.26, 95%CI 2.47-4.30), thrombocytes (HR 3.18, 95%CI 2.11-4.80) and leukocytes (HR 2.50, 95%CI 1.99-3.14). Patients in whom no laboratory tests were performed had a significantly decreased mortality risk in comparison with patients whose laboratory results were within reference range. For instance, hazard ratio for patients without a sodium measurement was 0.36 (95%CI 0.26-0.52) as compared to patients with a sodium measurement within reference range.

Table 2: Cox regression model for the association between predictors and 90-day mortality in older patients visiting the ED

ED characteristics	Events[a] (Total)	Univariate		Multivariate	
		HR (95%CI)	p-value	HR (95%CI)	p-value
Age	347 (3291)	1.06 (1.04-1.08)	<0.001	1.06 (1.04-1.08)	<0.001
Sex					
Female	173 (1748)	ref	ref	ref	ref
Male	174 (1543)	1.14 (0.93-1.41)	0.219	1.15 (0.92-1.43)	0.231
Time of ED visit					
Day 08.00h-15.59h	165 (1677)	ref	ref	ref	ref
Evening 16.00h-23.59h	127 (1254)	1.03 (0.82-1.30)	0.799	0.98 (0.77-1.24)	0.857
Night 00.00h-07.59h	55 (360)	1.62 (1.19-2.20)	0.002	1.27 (0.91-1.78)	0.163
Way of arrival[b]					
Self-referral	58 (654)	ref	ref	ref	ref
Brought in by ambulance	157 (1159)	1.58 (1.17-2.13)	0.003	1.33 (0.95-1.84)	0.096
General practitioner	102 (1108)	1.04 (0.75-1.43)	0.833	0.91 (0.64-1.29)	0.596
LUMC internal	23 (338)	0.75 (0.46-1.22)	0.243	0.81 (0.49-1.35)	0.424
Other Hospital	7 (28)	3.04 (1.39-6.66)	0.005	2.74 (1.22-6.11)	0.014
Presentation					
Limb problems	37 (608)	ref	ref	ref	ref
Unwell	99 (598)	2.93 (2.01-4.28)	<0.001	1.99 (1.23-3.20)	0.005
Chest pain	20 (346)	0.96 (0.56-1.65)	0.882	0.54 (0.29-1.00)	0.051
Shortness of breath	56 (304)	3.22 (2.13-4.88)	<0.001	1.43 (0.83-2.45)	0.195
Abdominal pain	26 (214)	2.09 (1.26-3.45)	0.004	1.68 (0.98-2.89)	0.061
Collapsed	19 (168)	1.96 (1.13-3.42)	0.017	1.29 (0.68-2.44)	0.439
Falls	10 (122)	1.38 (0.69-2.77)	0.369	1.19 (0.58-2.45)	0.663
Wounds	8 (108)	1.22 (0.57-2.62)	0.610	1.47 (0.67-3.21)	0.332
Palpitations	3 (101)	0.49 (0.15-1.58)	0.229	0.36 (0.11-1.26)	0.110
Other	69 (722)	1.61 (1.08-2.40)	0.019	1.44 (0.93-2.23)	0.100
Consulting medical specialty	99 (1371)	ref	ref	ref	ref
Surgical	248 (1920)	1.85 (1.47-2.34)	<0.001	1.55 (1.13-2.14)	0.007
Non-surgical					
Systolic BP, mmHg					
≤100	18 (109)	1.62 (1.00-2.61)	0.049	1.05 (0.64-1.72)	0.849
101-199	250 (2313)	ref	ref	ref	ref
≥200	16 (101)	1.52 (0.92-2.52)	0.104	1.15 (0.69-1.94)	0.589
Not measured	63 (768)	0.75 (0.57-0.99)	0.044	1.55 (0.79-3.02)	0.202
Heart rate, /min					
≤50	5 (55)	0.90 (0.37-2.17)	0.807	0.67 (0.27-1.68)	0.394
51-100	214 (2093)	ref	ref	ref	ref
101-110	28 (187)	1.48 (1.00-2.20)	0.049	1.20 (0.80-1.80)	0.375
111-129	27 (144)	1.93 (1.30-2.89)	0.001	1.46 (0.94-2.27)	0.090
≥130	12 (92)	1.29 (0.72-2.31)	0.392	1.41 (0.76-2.61)	0.277
Not measured	61 (720)	0.83 (0.62-1.10)	0.192	1.51 (0.72-3.14)	0.272

Table 2: Cox regression model for the association between predictors and 90-day mortality in older patients visiting the ED (*continued*)

ED characteristics	Events[a] (Total)	Univariate		Multivariate	
		HR (95%CI)	p-value	HR (95%CI)	p-value
Respiratory rate, /min					
≤8	1 (5)	2.65 (0.36-19.38)	0.337	2.07 (0.27-15.66)	0.481
9-14	33 (381)	ref	ref	ref	ref
15-20	95 (907)	1.21 (0.82-1.80)	0.343	1.15 (0.77-1.71)	0.507
21-29	68 (417)	1.95 (1.29-2.96)	0.002	1.63 (1.06-2.52)	0.027
≥30	31 (99)	4.16 (2.55-6.80)	<0.001	2.21 (1.25-3.92)	0.007
Not measured	119 (1482)	0.92 (0.62-1.35)	0.650	0.95 (0.61-1.47)	0.819
Oxygen saturation, %					
≤90	22 (81)	3.08 (1.99-4.78)	<0.001	1.96 (1.19-3.23)	0.008
91-94	43 (218)	2.09 (1.51-2.90)	<0.001	1.63 (1.16-2.31)	0.005
≥95	218 (2217)	ref	ref	ref	ref
Not measured	64 (775)	0.84 (0.63-1.11)	0.212	1.22 (0.65-2.27)	0.534
Temperature , ^{0}C					
≤34.9	14 (42)	3.43 (2.00-5.89)	<0.001	2.27 (1.28-4.01)	0.005
35.0-38.4	230 (2023)	ref	ref	ref	ref
≥38.5	14 (149)	0.82 (0.48-1.40)	0.461	0.43 (0.24-0.75)	0.003
Not measured	89 (1077)	0.72 (0.57-0.92)	0.009	1.12 (0.81-1.54)	0.498
Pain score, NRS					
0-3	181 (1645)	ref	ref	ref	ref
4-6	110 (1136)	0.87 (0.68-1.10)	0.240	1.24 (0.95-1.61)	0.114
7-10	36 (337)	0.97 (0.68-1.38)	0.847	1.55 (1.03-2.32)	0.034
Not measured	20 (173)	1.06 (0.67-1.68)	0.811	0.93 (0.58-1.49)	0.754
Blood tests[c]					
None performed	29 (770)	ref	ref	ref	ref
Performed	318 (2521)	3.52 (2.41-5.15)	<0.001	3.44 (2.13-5.56)	<0.001

Abbreviations: ED: Emergency Department, HR: hazard ratio, CI: confidence interval, ref: reference category, NRS: numeric rating scale.

[a.] 'Events' represent the number of deaths in each category within 90 days after ED admittance**.** [b.] Way of arrival was unknown in 4 patients (data not shown). No patients died in this category. Univariate Cox regression analysis showed HR 0.91 (95%CI 0.80-1.04; P value 0.178). Multivariate Cox regression analysis showed HR 0.00 (95%CI 0.00-9.37*10^{102}; P-value 0.947). [c.] Blood tests included haemoglobin, thrombocytes, leukocytes, C-reactive protein, sodium, potassium, creatinine, urea, troponin T and/or non fasted glucose.

Table 3: The association between laboratory results and 90-day mortality in older patients visiting the ED

		Univariate Cox Regression Analysis	
	Events[a] (Total)	HR (95%CI)	p-value
Haemoglobin			
Within reference range (male: 8.5-11.0, female: 7.5-10.0 mmol/L)	147 (1458)	ref	ref
Below reference range	158 (965)	1.66 (1.33-2.08)	<0.001
Above reference range	5 (37)	1.39 (0.57-3.38)	0.472
Not measured	37 (831)	0.43 (0.30-0.61)	<0.001
Thrombocytes			
Within reference range (150-400*10^9/L)	188 (1402)	ref	ref
Below reference range	46 (242)	1.45 (1.05-2.01)	0.023
Above reference range	26 (71)	3.18 (2.11-4.80)	<0.001
Not measured	87 (1576)	0.39 (0.31-0.51)	<0.001
Leukocytes			
Within reference range (4.00-10.00*10^9/L)	128 (1523)	ref	ref
Below reference range	11 (65)	2.10 (1.14-3.89)	0.018
Above reference range	171 (872)	2.50 (1.99-3.14)	<0.001
Not measured	37 (831)	0.52 (0.36-0.75)	<0.001
C-reactive protein			
Within reference range (0.0-5.0 mg/L)	88 (1102)	ref	ref
Above reference range	214 (1244)	2.25 (1.75-2.88)	<0.001
Not measured	45 (945)	0.58 (0.41-0.83)	0.003
Sodium			
Within reference range (136-144 mmol/L)	208 (1862)	ref	ref
Below reference range	65 (391)	1.53 (1.16-2.02)	0.003
Above reference range	37 (165)	2.14 (1.51-3.03)	<0.001
Not measured	37 (873)	0.36 (0.26-0.52)	<0.001
Potassium			
Within reference range (3.6-4.8 mmol/L)	200 (1804)	ref	ref
Below reference range	35 (162)	2.12 (1.48-3.03)	<0.001
Above reference range	58 (304)	1.78 (1.33-2.38)	<0.001
Not measured	54 (1021)	0.46 (0.34-0.63)	<0.001
Creatinine			
Within reference range (64-104 µmol/L)	127 (1258)	ref	ref
Below reference range	57 (475)	1.20 (0.88-1.64)	0.247
Above reference range	124 (685)	1.87 (1.46-2.40)	<0.001
Not measured	39 (873)	0.43 (0.30-0.61)	<0.001
Urea			
Within reference range (2.5-7.5 mmol/L)	95 (1199)	ref	ref
Below reference range	1 (1)	20.72 (2.88-148.92)	0.003
Above reference range	214 (1213)	2.34 (1.83-2.97)	<0.001
Not measured	37 (878)	0.52 (0.35-0.76)	0.001
Troponin T			
Within reference range (0.000-0.050 µg/L)	146 (1484)	ref	ref
Above reference value	77 (268)	3.26 (2.47-4.30)	<0.001
Not measured	124 (1539)	0.80 (0.63-1.02)	0.066

Table 3: The association between laboratory results and 90-day mortality in older patients visiting the ED (*continued*)

		Univariate Cox Regression Analysis	
	Events[a] (Total)	**HR (95%CI)**	**p-value**
Non-fasted glucose			
Within reference range (3.1-11.0 mmol/L)	249 (2123)	ref	ref
Below reference range	2 (7)	2.83 (0.70-11.39)	0.143
Above reference range	55 (253)	2.04 (1.52-2.73)	<0.001
Not measured	41 (908)	0.37 (0.27-0.52)	<0.001

Abbreviations: mmol: millimol, L: liter, mg: milligram, HR: hazard ratio, CI: confidence interval.
'Events' represent the number of deaths in each category within 90 days after ED admittance.

DISCUSSION

The main finding of the present study is that routinely, at entrance assessed, clinical parameters can be used to predict 90-day mortality in older persons admitted to the Emergency Department (ED). Independent predictors of 90-day mortality risk included: increasing age, referral by another hospital, disease presentation categorised as 'unwell', allocation to a non-surgical specialty, low respiratory rate, low oxygen saturation, body temperature and the performance of blood tests. In addition, abnormal laboratory results, which become known at a later stage during an ED visit, are univariablely associated with increased mortality risk. Patients for whom no laboratory tests were performed showed a decreased mortality risk.

Potential predictors of poor outcome in acutely presenting older adults have been studied before. Like in our study, increasing age was shown to associate with in-hospital mortality[21], as well as mortality risk 1-year after presentation[22]. Our research aimed at predictors known upon or soon after arrival of a patient at the ED in order to investigate their potential for new screening instruments. Other researchers also included predictors to their models that become available at a later stage during an ED visit, such as length of stay at the ED[21, 22]. Kennelly *et al.* found an association between arrival by ambulance and mortality, whereas our study did not[22]. Van Walraven *et al.* developed the hospital-patient one-year mortality risk (HOMR) model[23]. The HOMR model assesses 1-year mortality risk for adults ≥18 years who are acutely hospitalised, but it was not validated for ED visitors who were directly discharged without admittance to an inpatient ward. In addition, previous research shows that abnormal vital signs at triage associate with intensive care unit admission and in-hospital mortality in patients from the age of 16[24] as well as in older patients from the age of 75[25]. Furthermore, a high Modified Early Warning Score can be used to predict a worse in-hospital stay (e.g. mortality and hospitalisation) in older adults[7]. Our study demonstrates that respira-

tory rate, oxygen saturation, body temperature and pain score associate with 90-day mortality independent of other risk factors. Systolic blood pressure and heart rate did not remain significantly associated with mortality in the multivariable model. However, anatomical and physiological changes that occur with ageing may limit older people to generate an adequate response to injury[26]. As a consequence, some vital signs may not be reliable in reflecting the actual condition of an older patient[25].

Managing older people in the ED can be complex because of atypical disease presentation, polypharmacy and multiple comorbidities. Risk factors for adverse health outcomes include functional dependence, lack of social support and cognitive impairment[2]. Many risk factors and frailty screening tools such as the 'Identification of Seniors at Risk' have been evaluated in their ability to predict health outcome in older adults. Individually, they all lack sufficient prognostic accuracy to identify patients at high risk for poor outcome[27]. We found that routinely collected clinical parameters associate with mortality in older patients admitted to the ED. Although this is not unexpected, it implies that early assessed characteristics of an ED visit are not only of value with respect to short term outcomes, but may be useful when considering the period after discharge as well. Models including both disease specific parameters (for example respiratory rate) and parameters reflecting functional and cognitive status may give rise to a more complete assessment of the older individual. Our findings lay ground for creating new prediction models using routinely collected parameters alongside frailty characteristics in order to adequately predict outcome in acutely presenting older patients. We are currently performing prospective studies to develop and validate such predictive models with respect to multiple negative endpoints such as mortality, admission rate, quality of life and functional status (www.apop.eu[28]). These prediction models should be able to detect patients at high risk for poor outcome and enable the development of appropriate interventions to improve acute medical care for older patients.

The present study was limited by its retrospective nature and could not provide reliable information on frailty characteristics such as multi-morbidity, polypharmacy and functional and cognitive impairment and these characteristics could not be studied in our model. However, it is unlikely that the investigated predictors in our study would change when collected in a prospective matter. Our study was set at a single centre tertiary referral hospital which may make our results less generalisable. Strong points of our study were the large sample size of over three thousand ED visits, the use of universal predictors that were likely to be free of bias and the fact that mortality is a very robust end point of which data were available for all patients through municipality records. Our study is unique in the fact that we investigated predictors early known during an ED visit which may be suitable for a screening instrument.

A proper screening instrument that identifies older patients at risk of poor outcome is the first step towards changing outcome. We aim that a screening instrument will enable

us to set up special care trajectories in order to improve recovery after acute presentation at the ED. These tailored trajectories could include extra attention on rehabilitation, prevention of delirium and advanced care planning and are currently investigated in a prospective study concerning the acutely presenting older patient ('APOP-study').
To conclude, routinely collected parameters of older persons attending the ED can be used to predict 90-day mortality. This survey constitutes preparatory work towards creating a proper screening instrument for predicting and improving health outcome in acutely presenting older patients.

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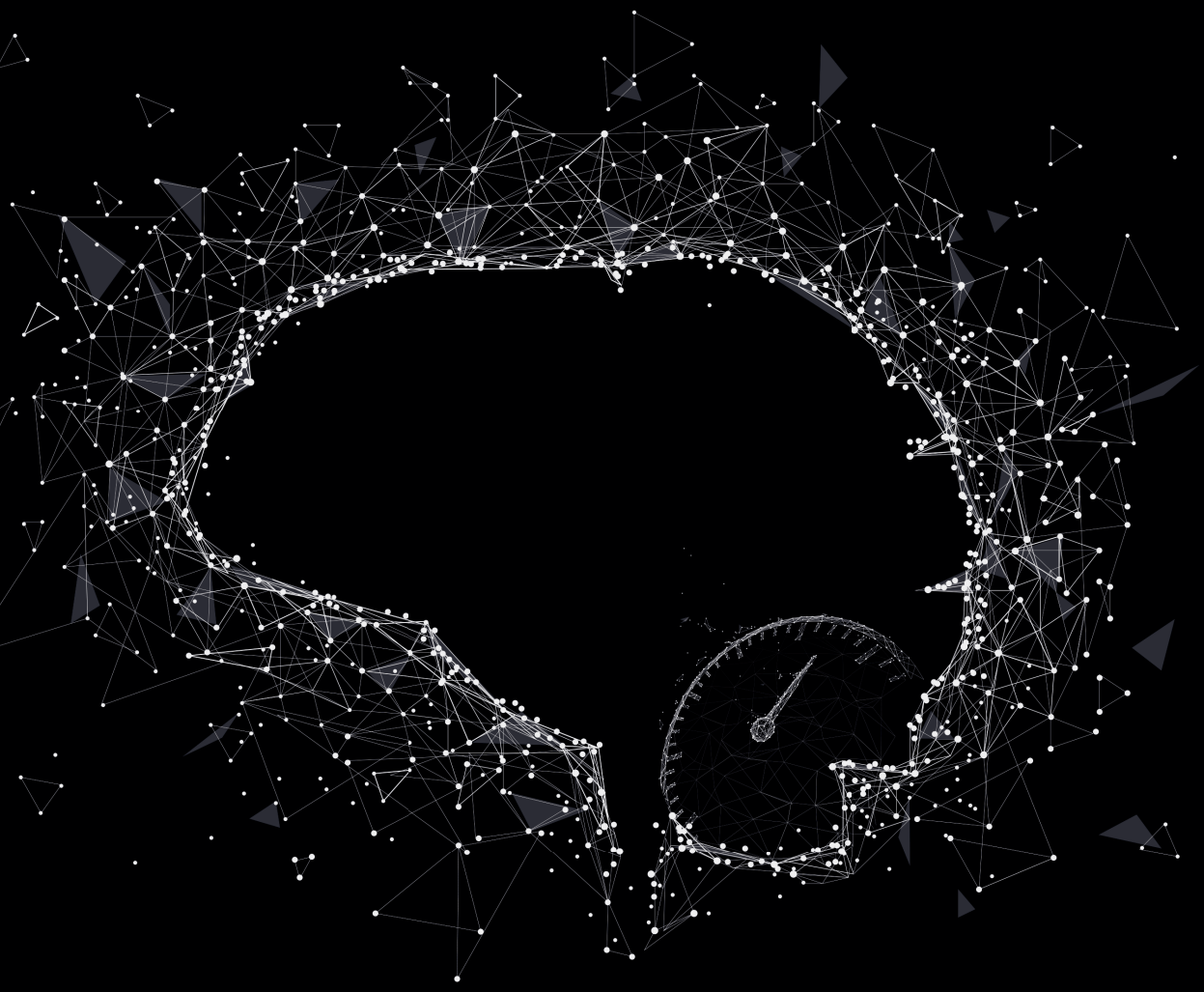

Chapter 5

Prediction of 90-day mortality in older ED patients

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Early prediction of hospital admission for Emergency Department patients, a comparison between patients younger or older than 70-years

ABSTRACT

Introduction: The aim of this study was to develop models that predict hospital admission of Emergency Department patients in patients younger and older than 70 and compare their performance.

Methods: Prediction models were derived in a retrospective observational study of all patients ≥18-years old visiting the Emergency Department (ED) of a university hospital during the first 6 months of 2012. Patients were stratified into two age groups (<70-years old, ≥70-years old). Multivariable logistic regression analysis was used to identify predictors of hospital admission among factors available immediately after patient arrival to the ED. Validation of the prediction models was performed on patients presenting to the ED during the second-half of the year 2012.

Results: 10.807 patients were included in the derivation and 10.480 in the validation cohorts. Strongest independent predictors of hospital admission among the 8728 patients <70-years old were age, sex, triage category, mode of arrival, performance of blood tests, chief complaint, ED revisit, type of specialist, phlebotomised blood sample, and all vital signs. Area under the curve (AUC) of the validation cohort for those <70-years old was 0.86 (95%CI 0.85-0.87). Among the 2079 patients ≥70-years the same factors were predictive except for gender, type of specialist and heart rate; the AUC was 0.77 (95%CI 0.75-0.79). The prediction models could identify a group of 10% patients with the highest risk in whom hospital admission was predicted at ED triage with a positive predictive value (PPV) of 71% (95%CI 68-74%) in younger and PPV 87% (95%CI 81-92%) in older patients.

Conclusion: Demographic and clinical factors readily available early in the ED visit can be useful in identifying patients who are likely to be admitted to hospital. While the model for the younger patients had a higher AUC, the model for older patients had a higher PPV in identifying the patients at highest risk for admission. Of note, heart rate was not a useful predictor in the older patients.

INTRODUCTION

Older adults presenting to Emergency Departments (EDs) for medical care frequently are admitted to the hospital[1-4]. Despite a high probability of admission, they are at risk of having prolonged length of stay in the ED, which increases the chance of in-hospital adverse events[5]. If ED physicians had an accurate decision-making tool they could use early during the ED visit to predict which older patients have the highest probability of being admitted using routinely available demographic and clinical factors available at triage, ED length of stay might be reduced. Interventions to expedite the admission of older patients might also improve health-related and ED flow and function outcomes. Such a tool however, is not yet available[6]. It also is not yet known if demographic and clinical factors predictive of hospital admission are the same for both older and younger ED patients, and if decision-making tools comprised of these factors perform equally well for both age groups.

Independent predictors of hospital admission of ED patients have been identified[7] previously, yet mainly reflect disease severity. The Modified Early Warning Score (MEWS) [8] is frequently used to quantify disease severity and can predict probability of hospital admission[9] disposition[10] and mortality[11] of ED patients. However, physiology, polypharmacy and multiple comorbidities of older patients affect measured vital signs and delay recognition of serious disease; when relying solely on vital signs a proportion of severely ill older patients requiring admission will not be identified[12]. Given the discrepancy in the utility of hospital admission prediction models using vital signs and disease severity when they are applied to different age groups, tools helping to predict need for admission based on other clinical characteristics also might not be equally useful for older and younger ED adult patients. If this is the case, different prediction rules should be derived and used based on patient age.

The goal of this study was therefore to derive prediction models separately for older and younger adults which identify need for hospital admission, using routinely demographic and clinical data available at ED triage. We further aimed to assess how well these prediction models performed for these two age groups. The ultimate aim for this prediction model was for its eventual application in identifying early which patients would be admitted from the ED, potentially improving efficiency of care pathways and reducing ED length of stay.

METHODS

Study design and setting

This investigation involved deriving and validating a hospital admission prediction rule for adult ED patients. Data were obtained retrospectively from the ED of the Leiden University Medical Center (LUMC), which is a tertiary care hospital with an annual census of approximately 30.000 ED visits. LUMC has an Acute Medical Unit (13 beds) designed to accept admissions from the ED. The Medical Ethics Committee waived the need for informed consent because data were collected as part of past clinical care and de-identified after extraction from the patient files.

Selection of participants

Inclusion criteria

We included all ED visits by adults ≥18-years old to LUMC between January 1, 2012 and December 31, 2012. ED patients who presented between January 1 – June 30 were included in the derivation cohort, while those presenting July 1 – December 31 were included in the validation cohort.

Exclusion criteria

Patients who arrived to the ED undergoing cardiopulmonary resuscitation or classified as Manchester Triage System[13] (MTS) category 'red' (needing immediate care) were excluded because their likelihood of hospital admission was so great that a prediction tool would not be needed for this population. Patients who died in the ED and those who left without being evaluated also were excluded. In addition, patients with ED visits due to logistical reasons were excluded, such as those attending for a planned re-evaluation because they could not wait until the next available out-patient clinic appointment, visits to the ED because of lack of availability of time in the out-patient clinic, laboratory checks for logistical reasons and patients who were sent away from the ED to visit their GP (figure 1). For this, a pre-defined list of objective criteria, based on expert opinion, was used. Patient files were checked by a single researcher (JAL) to assess exclusion criteria.

Study protocol and measurements

Data were automatically harvested from the electronic patient files (Chipsoft-EZIS®, version 5.2, 2006-2014, Amsterdam, The Netherlands) using an application designed by the LUMC department of Information Technology. One investigator (JAL) checked the data for validity and corrected typing errors. This was performed by reference to medical records in case of outliers. Furthermore using sampling JAL checked patient records to assess if study data was adequately withdrawn from the patients files. The data were not

extracted manually and not subject to interpretation. Therefore, a measure of inter-rater variability is not applicable.

Because the aim of this investigation was to develop a tool, using data readily available at triage, the following data were collected: age, sex, Manchester Triage System (MTS) triage category, chief complaint, mode of arrival to ED, type of specialist, ED visits within prior 30 days, indication for phlebotomised blood sample testing and vital signs. These variables were chosen by the study authors based on clinical judgement, frequently used variables in similar research[14-16], their availability upon patient arrival to the ED and inclusion in the ED electronic medical records. A detailed description of the collection of all variables can be found in Supplemental Material (available trough http://dx.doi.org/10.1136/emermed-2016-205846).

Outcomes

The primary endpoint of this study was hospital admission, defined as either admission to the LUMC or transfer to another hospital for admission. This outcome was downloaded directly from the patient files.

Data Analysis

Patients were divided into two age groups for analysis, <70-years and ≥70-years old, in line with the age cut-off used in government initiated interventions in The Netherlands[17]. Data were summarized as number and percentages or means and standard deviation for normally distributed variables, or as medians with interquartile range for non-normally distributed variables, as appropriate. Missing measurements of vital signs were handled as a separate category and analysed alongside categories of measured values, for example oxygen saturation has 4 categories: <90%, 91-94%, ≥95% and missing, where the reference category is ≥95%. Student's t-tests assuming independence were used to compare groups for normally distributed variables and Mann-Whitney-U tests for non-normally distributed variables. Chi-square tests were used for categorical variables. Univariable binary logistic regression was used to assess possible predictors of hospital admission using demographic and clinical characteristics extracted from the medical records. Age (<70-years old or ≥70-years-old) as an effect modifier of the relationship between variables in the model and the outcome of hospital admission was tested in the univariable analyses. Multivariable binary logistic regression was used to create an optimal model. Odds Ratios (ORs) and corresponding 95% confidence intervals (CIs) were estimated. Risks associated with age were expressed per 10 year age groups. The general rule of thumb that at least 10 events per predictor variable are needed to prevent over-fitting of the model was used. Because the database contained more than 3000 hospital admissions all potential predictor variables could be incorporated in the model[18].

An optimal model was created for each age group, using backward elimination with Akaike's Information Criterion to eliminate predictors from the model, with a cut-off point of $p<0.05$. This made the model as small as possible whilst still containing all clinically relevant parameters. Goodness of fit was tested using the Hosmer-Lemeshow test, this was performed ten times in a random subsample of 1000 patients.

This method standardized the power of the Hosmer-Lemeshow test to prevent overpowering caused by the large number of study subjects[19].

Receiver operator characteristics curves were drafted and area under the curve (AUC) estimated to measure the discriminative performance of the models. Temporal validation of the models were performed using data collected from the second-half of 2016. Calibration of the models in the validation cohort was assessed using calibration plots.

The distribution of risk of admission per age group was calculated for the validation cohort using the following equation: $\frac{1}{1+e^{(\text{intercept}+\text{linear predictor})}}$. The individual risk of each patient was calculated and ranked. The 10% of the ED patient population, per age group, with the highest chance of hospital was designated 'high risk'. This was deemed a clinically relevant and feasible cut-off point for risk of admission, for which sensitivity, specificity, positive predictive value, negative predictive value were calculated.

As a sensitivity analysis, the alternative clinically relevant vital sign cut-off values were assessed as predictors in the models and their discriminative performance and calibration were re-assessed. In a second sensitivity analysis, we created a multivariable model using the whole year 2012 (without dividing the year into successive six-month blocks of time) and randomly selected a training and test cohort to assess for introduction of bias due to the temporal validation.

Statistical significance was set at the alpha=0.05 level for all analyses. All statistical analyses were performed using IBM SPSS Statistics package (version 23, New York, USA).

RESULTS

Characteristics of study subjects

In 2012, there were 27.862 visits to the LUMC ED, of which 21.287 were included in this analysis (figure 1). The 6575 excluded patients were due to ED use for logistical reasons or arrival during CPR (n=1486), patients aged ≤18-years (n=4802) or patients with red triage or who deceased (n=287).

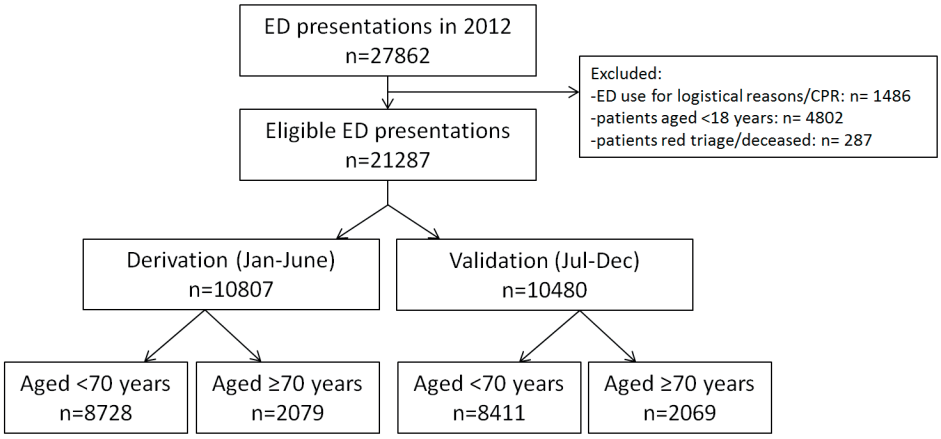

Figure 1: Flowchart of participant selection.

Baseline characteristics of the study population stratified by age group are shown in table 1. The distribution of demographics and clinical characteristics by age group were similar within the derivation and validation cohorts.

In the derivation cohort, 2014 (23.1%) younger patients and 898 (43.2%) older patients were admitted to the hospital. In the validation cohort, 2030 (24.1%) younger patients and 919 (44.4%) older patients were admitted. Baseline characteristics between patients in the derivation cohort admitted to hospital and those discharged are shown in table 2.

Table 1: Baseline characteristics of study population

	Derivation			**Validation**		
Baseline features	**<70-years** n=8728	**≥70-years** n=2079	**p value**	**<70-years** n=8411	**≥70-years** n=2069	**p value**
Age, median IQR	44.8 (28.8-57.4)	78.1 (73.9-83.6)		44.8 (28.4-58.0)	77.9 (73.9-83.0)	
Male, *n (%)*	4762 (54.6)	995 (47.9)	<0.001	4597 (54.7)	1044 (50.5)	0.001
Triage category, *n (%)*			<0.001			<0.001
<10 minutes	1921 (22.0)	657 (31.6)		1893 (22.5)	683 (33.0)	
<1 hour	3567 (40.9)	943 (45.4)		3557 (42.3)	966 (46.7)	
<2 hour	3205 (36.7)	472 (22.7)		2921 (34.7)	410 (19.8)	
<4 hours	35 (0.4)	7 (0.3)		40 (0.5)	10 (0.5)	
Arrival mode, *n (%)*			<0.001			<0.001
Self-referral	4258 (48.8)	467 (22.5)		3794 (45.1)	404 (19.5)	
Ambulance/other institution	1316 (15.1)	596 (28.7)		1659 (19.7)	833 (40.3)	
Referred by GP/specialist	3154 (36.1)	1016 (48.9)		2958 (35.2)	832 (40.2)	

Table 1: Baseline characteristics of study population (*continued*)

	Derivation			Validation		
Baseline features	**<70-years** n=8728	**≥70-years** n=2079	**p value**	**<70-years** n=8411	**≥70-years** n=2069	**p value**
Type of specialist			<0.001			<0.001
Medicine	3809 (43.6)	1251 (60.2)		3732 (44.4)	1245 (60.2)	
Surgery	4919 (56.4)	828 (39.8)		4679 (55.6)	824 (39.8)	
Revisit to the ED, *n (%)*			0.082			0.071
Visit <30 days	922 (10.6)	247 (11.9)		873 (10.4)	243 (11.7)	
Chief complaint[a]			<0.001			<0.001
Minor trauma	3656 (42.2)	621 (30.1)		3301 (39.6)	641 (31.2)	
Major trauma	183 (2.1)	32 (1.5)		208 (2.5)	28 (1.4)	
Chest pain	980 (11.3)	302 (14.6)		992 (11.9)	329 (16.0)	
Dyspnea	426 (4.9)	221 (10.7)		394 (4.7)	179 (8.7)	
Syncope	219 (2.5)	118 (5.7)		241 (2.9)	100 (4.9)	
Psychiatric complaints	219 (2.5)	34 (1.6)		230 (2.8)	26 (1.3)	
Malaise	1032 (11.9)	377 (18.3)		1034 (12.4)	403 (19.6)	
Abdominal pain	935 (10.7)	183 (8.9)		922 (11.1)	183 (8.9)	
Other	1018 (11.7)	177 (8.6)		1019 (12.2)	164 (8.0)	
Testing, *n (%)*			<0.001			<0.001
Phlebotomised blood sample	4714 (54.0)	1606 (77.2)		4583 (54.5)	1599 (77.3)	
Vital signs						
Systolic BP, mmHg[b]	136 (21.4)	145 (27.3)	<0.001	135 (21.5)	145 (28.1)	<0.001
0_2 saturation, %[c] *median, IQR*	98 (98-100)	98 (96-100)	<0.001	99 (97-100)	98 (96-99)	<0.001
Temperature, °C[d]	37.0 (0.8)	36.9 (1.0)	<0.001	37.0 (0.8)	36.9 (0.9)	<0.001
Respiratory rate, /min[e]	17.6 (4.6)	18.7 (5.5)	0.007	17.6 (4.8)	18.6 (5.4)	<0.001
Heart rate, /min[f]	86 (20)	84 (20)	<0.001	86 (21)	84 (21)	<0.001

Values are mean, standard deviation unless noted otherwise.
Abbreviations: SD: standard deviation, n:number, IQR: interquartile range, GP: general practitioner, min: minute.
Vital parameters measured are: 0_2: oxygen saturation, measured in percentage oxygenated haemoglobin. Systolic BP: Systolic blood pressure, measured in millimetres of mercury. Temperature measured in degrees Celsius. Heart rate and respiratory rate are measured as times per minute.
Number of measured values per age group: <70-years: a: n=17.009, b: n=9924, c: n=10.018, d: n=9953, e: n=5807, f: n=10.371. ≥70-years: a :n=4118, b: n=3232, c: n=3208, d: n=2890, e :n=2302, f: n=3292.
P-values are measured by t-test for scale values and chi-square for categorical values. Mann-Whitney U test for non-parametric variables.

Table 2: Baseline characteristics of study population, the derivation cohort stratified around hospital admission

	<70-years			>70-years		
	Discharged	**Admitted**	**p**	**Discharged**	**Admitted**	**p**
Baseline features	n=6714	n=2014	**value**	n=1181	n=898	**value**
Age, median IQR	41.9	52.4	<0.001	78.1	78.1	0.280
	(26.8-55.6)	(40.0-62.0)		(73.7-83.4)	(74.2-83.7)	
Male, *n (%)*	3625 (54.0)	1137 (56.5)	0.052	529 (44.8)	466 (51.9)	0.001
Triage category, *n (%)*			<0.001			<0.001
<10 minutes	1066 (15.9)	855 (42.5)		270 (22.9)	387 (43.1)	
<1 hour	2609 (38.9)	958 (47.6)		530 (44.9)	413 (46.0)	
<2 hour	3007 (44.8)	198 (9.8)		374 (31.7)	98 (10.9)	
<4 hours	32 (0.5)	3 (0.1)		7 (0.6)	0 (0)	
Arrival mode, *n (%)*			<0.001			<0.001
Self-referral	3648 (54.3)	610 (30.3)		303 (25.7)	164 (18.3)	
Ambulance/other institution	782 (11.6)	534 (26.5)		287 (24.3)	309 (34.4)	
Referred by GP/specialist	2284 (34.0)	870 (43.2)		591 (50.0)	425 (47.3)	
Type of specialist			<0.001			<0.001
Medicine	2430 (36.2)	1379 (68.5)		605 (51.2)	646 (71.9)	
Surgery	4284 (63.8)	635 (31.5)		576 (48.8)	252 (28.1)	
Revisit to the ED, *n (%)*			<0.001			
Visit <30 days	595 (8.9)	327 (16.2)		118 (10.0)	129 (14.4)	0.002
Chief complaint[a]			<0.001			<0.001
Minor trauma	3370 (50.6)	286 (14.3)		456 (39.0)	165 (18.4)	
Major trauma	103 (1.5)	80 (4.0)		11 (0.9)	21 (2.3)	
Chest pain	764 (11.5)	216 (10.8)		215 (18.4)	87 (9.7)	
Dyspnea	238 (3.6)	188 (9.4)		93 (7.9)	128 (14.3)	
Syncope	141 (2.1)	78 (3.9)		64 (5.5)	54 (6.0)	
Psychiatric complaints	127 (1.9)	92 (4.6)		13 (1.1)	21 (2.3)	
Malaise	526 (7.9)	506 (25.3)		136 (11.6)	241 (26.9)	
Abdominal pain	592 (8.9)	343 (17.1)		81 (6.9)	102 (11.4)	
Other	804 (12.1)	214 (10.7)		101 (8.6)	76 (8.5)	
Performed test, *n (%)*			<0.001			<0.001
Phlebotomised blood sample	2868 (42.7)	1846 (91.7)		747 (63.3)	859 (95.7)	
Vital signs						
Systolic BP, mmHg[b]	138 (20)	135 (23)	<0.001	148 (27)	142 (27)	<0.001
0_2 saturation, %[c] *median, IQR*	99 (98-100)	99 (97-100)	<0.001	98 (96-100)	98 (95-99)	<0.001
Temperature, °C[d]	36.9 (0.7)	37.2 (1.1)	<0.001	36.8 (0.6)	37.1 (1.2)	<0.001
Respiratory rate, /min[e]	16.9 (3.9)	18.6 (5.4)	<0.001	17.5 (4.3)	19.7 (6.1)	<0.001
Heart rate, /min[f]	83 (19)	91 (22)	<0.001	82 (21)	86 (20.7)	0.002

Values are mean, standard deviation unless noted otherwise.

Abbreviations: SD: standard deviation, n:number, IQR: interquartile range, GP: general practitioner, min: minute. Vital parameters measured are: 0_2: oxygen saturation, measured in percentage oxygenated haemoglobin. Systolic BP: Systolic blood pressure, measured in millimetres of mercury. Temperature measured in degrees Celsius. Heart rate and respiratory rate are measured as times per minute.

Number of measured values per age group <70-years: a:n=8668, b:n=5006, c:n=5000, d:n=4795, e:n=2895, f:n=5178, ≥70-years: a:n=2065, b:n=1589, c:n=1582, d:n=1434, e:n=1154, f:n=1614.

P-values are measured by t-test for scale values and chi-square for categorical values. Mann-Whitney U test for non-parametric variables.

Differences in baseline characteristics between the derivation and validation cohorts, stratified by age, can be found in supplemental table 1 (available trough http://dx.doi.org/10.1136/emermed-2016-205846).

Relationship of patient demographic and clinical factors to hospital admission

The univariable analyses examining the relationship between patient demographic and clinical characteristics and hospital admission stratified by the two age groups are provided in supplemental table 2. The factors associated with hospital admission were the same for both age groups (for example; urgent triage category, phlebotomised blood sample, fever) although the strength of the relationships differed for some factors between age groups. The variables in the final model for the younger patients are age, sex, triage category, arrival mode, chief complaint, ED revisit, type of specialist, phlebotomised blood sample, oxygen saturation, systolic BP, temperature, heart rate and respiratory rate. The variables in the final model for the older patients are triage category, arrival mode, chief complaint, type of specialist, phlebotomised blood sample, oxygen saturation, systolic BP, temperature and respiratory rate.

Table 3: Final multivariable models of hospitalisation of patients at the Emergency Department

	<70-years		≥70-years	
Predictor	**OR**	**95%CI**	**OR**	**95%CI**
Age/10	1.25	(1.19-1.30)		
Sex				
Male	1.25	(1.11-1.42)		
Female	ref	ref		
Triage category				
>1 hour	ref	ref	ref	ref
< 1 hour	2.22	(1.85-2.67)	1.72	(1.27-2.33)
< 10 min	3.64	(2.93-4.52)	3.15	(2.19-4.53)
Arrival mode				
Self- referral	ref	ref	ref	ref
Referred	1.21	(1.05-1.40)	1.09	(0.82-1.44)
Ambulance	1.94	(1.63-2.32)	1.40	(1.03-1.90)
Chief Complaint				
Minor trauma	ref	ref	ref	ref
Major trauma	1.31	(0.89-1.94)	0.90	(0.39-2.08)
Chest pain	0.28	(0.21-0.36)	0.19	(0.13-0.29)
Dyspnea	0.79	(0.58-1.07)	0.44	(0.28-0.68)
Syncope	0.74	(0.51-1.06)	0.52	(0.32-0.83)
Psychiatric	1.48	(1.03-2.13)	1.29	(0.59-2.84)

Table 3: Final multivariable models of hospitalisation of patients at the Emergency Department (*continued*)

Predictor	<70-years		≥70-years	
	OR	**95%CI**	**OR**	**95%CI**
Malaise	1.31	(1.03-1.66)	1.27	(0.90-1.78)
Abdominal pain	1.34	(1.07-1.68)	1.11	(0.74-1.66)
Other	1.13	(0.89-1.43)	1.23	(0.80-1.88)
Type of specialist				
Medicine	1.17	(0.99-1.37)		
Surgery	ref	ref		
Revisit to the ED	1.57	(1.32-1.88)	1.94	(1.41-2.67)
Phlebotomised blood sample	4.79	(3.83-5.99)	7.46	4.94-11.28
Oxygen saturation				
≤ 90%	1.80	(0.93-3.48)	4.26	1.77-10.25
91-94%	1.78	(1.26-2.51)	1.62	(1.04-2.52)
≥ 95%	ref	ref	ref	ref
Missing	1.11	(0.81-1.52)	1.14	(0.67-1.92)
Systolic BP				
≤100	1.96	(1.33-2.88)	1.67	(0.91-3.06)
101-199	ref	ref	ref	ref
>200	1.32	(0.70-2.47)	0.74	(0.41-1.32)
Missing	0.57	(0.40-0.82)	0.52	(0.30-0.89)
Temperature				
≤35.0	1.86	(0.89-3.87)	0.96	(0.36-2.56)
35.1-38.4	ref	ref	ref	ref
≥38.5	3.34	(2.41-4.61)	3.43	(1.82-6.47)
Missing	0.85	(0.70-1.02)	0.93	(0.69-1.25)
Heart rate				
≤50	0.67	(0.36-1.26)		
51 - 100	ref	ref		
101 -110	1.62	(1.29-2.03)		
111-129	1.57	(1.22-2.02)		
≥130	2.57	(1.76-3.74)		
Missing	1.07	(0.69-1.68)		
Respiratory rate				
≤8	0.75	(0.15-3.74)	2.37	(0.15-36.95)
9-14	ref	ref	ref	ref
15-20	0.94	(0.76-1.15)	1.04	(0.74-1.45)
21-29	1.29	(0.99-1.69)	1.74	(1.16-2.62)
≥30	3.98	(1.99-7.95)	4.41	(1.86-10.43)
Missing	1.05	(0.85-1.29)	0.99	(0.69-1.42)

Table 3: Final multivariable models of hospitalisation of patients at the Emergency Department (*continued*)

Predictor	<70-years		≥70-years	
	OR	**95%CI**	**OR**	**95%CI**
Intercept	-4.572		-2.623	
AUC (95%CI)	0.85	(0.84-0.86)	0.81	(0.79-0.82)
GoF-value	0.289		0.559	
Temporal validation AUC (95%CI)	0.86	(0.85-0.87)	0.77	(0.75-0.79)

Abbreviations: n: number, OR: odds ratio, 95%CI: 95% confidence interval. GoF= Hosmer-Lemeshow Goodness of Fit χ^2 test. AUC: Area under the curve. Age in years divided by ten.
Vital parameters measured are oxygen saturation, measured in percentage oxygenated haemoglobin. Systolic BP: Systolic blood pressure, measured in millimetres of mercury. Temperature measured in degrees Celsius. Heart rate and respiratory rate are measured as times per minute.
P-value values are derived from multiple logistic regression analysis.

Individual chance of hospital admission <70 years = $1/(1+\exp\left(-\left(-4.572+\left(0.220*\frac{\text{age}}{10}\right)+0.225*\right.\right.$
$\text{male}+0.798*\text{triage}<1\text{ hour}+1.292*\text{triage}<10\text{ min}+0.194*\text{self}-\text{referral}+0.664*$
$\text{ambulance}+0.273*\text{major trauma}+-1.282*\text{chestpain}+-0.238*\text{breathlessness}+-0.305*$
$\text{syncope}+0.391*\text{psychiatric}+0.269*\text{malaise}+0.294*\text{abdominal pain}+0.122*$
$\text{other complaint}+0.155*\text{medicine}+0.453*\text{revisit}+1.567*\text{blood drawn}+0.585*\text{sat}\leq 90\%+$
$0.576*\text{sat}91-94\%+0.103*\text{missing sat}+0.674*\text{BP}\leq 100+0.277*\text{BP}\geq 200+-0.558*$
$\text{BP missing}+0.619*\text{temp}\leq 35+1.205*\text{temp}\geq 38.5+-0.165*\text{temp missing}+-0.395*$
$\text{heartrate}\leq 50+0.481*\text{heartrate }101-110+0.450*\text{heartrate }111-129+0.943*\text{heartrate}\geq$
$130+0.071*\text{heartrate missing}+-0.290*\text{resp rate}\leq 8+-0.064*\text{resp rate }15-20+0.256*$
$\left.\left.\text{resp rate }21-29+1.380*\text{resp rate }\geq 30+0.047*\text{resp rate missing}\right)\right)\right)$

Individual chance of hospital admission ≥70 years $=1/(1+\exp(-(-2.623+0.541*\text{triage}<1\text{ hour}+$
$1.148*\text{triage}<10\text{ min}+0.086*\text{self}-\text{referral}+0.337*\text{ambulance}+-0.103*\text{major trauma}+$
$-1.640*\text{chestpain}+-0.829*\text{breathlessness}+-0.659*\text{syncope}+0.258*\text{psychiatric}+0.236*$
$\text{malaise}+0.102*\text{abdominal pain}+0.208*\text{other complaint}+0.663*\text{revisit}+2.010*$
$\text{blood drawn}+1.449*\text{sat}\leq 90\%+0.483*\text{sat}91-94\%+0.128*\text{missing sat}+0.511*\text{BP}\leq$
$100+-0.300*\text{BP}\geq 200+-0.655*\text{BP missing}+-0.037*\text{temp}\leq 35+1.232*\text{temp}\geq 38.5+$
$-0.071*\text{temp missing}+0.861*\text{resp rate}\leq 8+0.037*\text{resp rate }15-20+0.555*\text{resp rate }21-$
$29+1483*\text{resp rate}\geq 30+-0.014*\text{resp rate missing}))$

As shown in the results for the multivariable models by age groups (table 3), urgent triage category, hospital arrival by ambulance, indication for taking a phlebotomised blood sample, presenting complaint of "malaise", or a non-surgical problem, a systolic blood pressure below 100mmHg, oxygen saturation below 95%, fever or tachypnoea >30 breaths/min were associated with greater odds of hospital admission for both age groups. Chest pain, loss of consciousness and dyspnoea as a presenting complaint, as well as no measured blood pressure were associated with a significantly decreased odds of being admitted among older patients while in younger patients chest pain decreased the probability of hospital admission. In the sensitivity analyses, similar results were found for the relationship between patient demographic and clinical factors and hospital admission when a single model instead of separate models for the two age groups were used (supplemental table 3) and when a randomly selected training and test cohort were used for these comparisons (supplemental table 4).
The AUC of the prediction model for the derivation cohort for hospital admission among patients <70-years old was 0.85 (95%CI 0.84-0.86), which was higher than the AUC of the

prediction model for ≥70-years old (0.81 (95%CI 0.79-0.82). In the temporal validation cohort, the AUC for younger patients was 0.86 (95%CI 0.85-0.87), which also was higher than the model for older patients, which was 0.77 (95%CI 0.75-0.79).

The calibration plots in figure 2 show the observed hospital admission rate in relation to the predicted chance of hospital admission in the validation group. The Hosmer-Lemeshow Goodness of Fit-test in both groups was p>0.05, suggesting that predicted probabilities are in line with the observed and that the model fit the data well. In a sensitivity analysis using different cut-off points for vital signs in younger and older patients, there were no differences in the performance of either model.

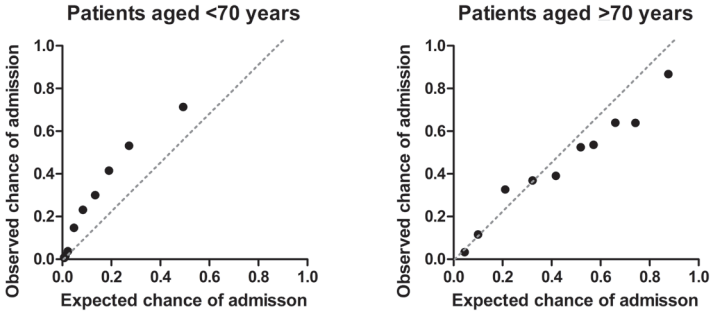

Figure 2: Calibration plot of expected and observed chance of admission for patients aged <70 and ≥70-years – validation cohort

As shown in figure 3, there were more younger adult patients with a lower predicted chance of hospital admission in the validation cohort than for the older adult group. The predicted chance of hospital admission was also more equally distributed among the older patients. Table 4 depicts the test performance parameters of the models in predicting hospital admission by age group. Specificity, PPV and LR+ were higher in older patients. The prediction model shows superior predictive applicability than for example triage category alone.

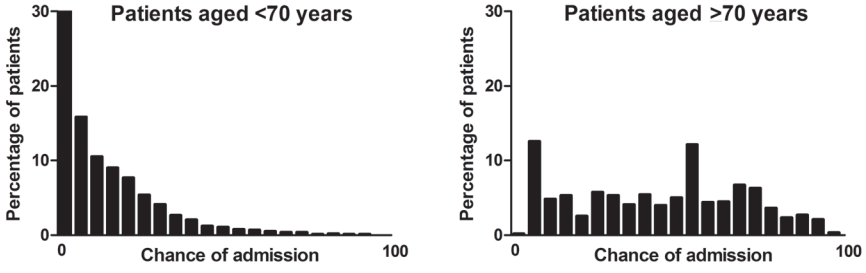

Figure 3: Distribution of chance of admission predicted by our model for patients aged <70 and ≥70-years – validation cohort

DISCUSSION

In this investigation, we found that routinely collected demographic and clinical patient data at ED triage can be used to predict hospital admission among ED patients. However, although the predictors of hospital admission are the same regardless of age groups, the strength of the relationships between patient demographic and clinical factors and hospital admission as well as the performance of the predictive models differ by age groups (<70-years-old vs. ≥70-years old). Overall predictive performance of the model was better for younger patients, although positive predictive value was higher among older patients.

Our findings are in concordance with prior studies[7, 9, 10, 14, 20]. Most of these variables, like triage category[13], chief complaint and abnormal vital signs[9], reflect illness severity at ED presentation. Sun *et al.*[14] derived a prediction model for hospital admission in over 300.00 ED patients in Singapore. It was validated using split-validation and the model used age, race, arrival mode, triage category, preceding hospital admission or ED visit and chronic conditions as predictors. The AUC of this model was 0.85, which is comparable to our findings. Cameron *et al.* created a similar prediction model in over 300.000 adult ED patients in Scotland. This prediction model used age, early warning score, triage category, referral and arrival mode and preceding hospital admission within one year and found an AUC of 0.88. A model by Meisel *et al.* in the United States to predict hospital admission in the pre-hospital phase used age and chief complaint as predictors and found an AUC of 0.80[20]. For all these studies, the investigators observed that age was an important factor in predicting hospital admission, however they did not compare the predictive properties of disease severity between the younger and older patients. A prediction model for hospitalisation for ED patients in 4873 patients ≥75-years-old by LaMantia *et al.*[21] , included injury severity, heart rate, diastolic blood pressure and patient chief complaint as predictors had an AUC of 0.73 (95%CI 0.69-0.76), with a sensitivity of 33%, specificity 88% and LR of 2.75. Our model performed better, possibly due to inclusion of more demographic and clinical characteristics. Also sample size, differences in care system and selection of patients could have influenced the performance of the models. Physiology, polypharmacy and multi-morbidity affects the measured vital signs of older patients, and some studies indicate that when relying solely on vital signs a proportion of severely ill older patients will be missed[12]. To address this concern, we assessed whether the predictors of hospital admission are different for older as compared to younger adult ED patients. In our model for older patients, age was not a predictor. One explanation for this observation may be that by limiting the age range to those 70-years old and older to assess the predictive value of age there was limited contrast in this population and hence a lack of power to detect differences by age. As an alternative explanation, among older patients disease sever-

ity and geriatric factors (e.g. pre-existing functional or cognitive impairment) are more important than calendar age. As shown in table 2 there is no difference between median age for patients hospitalised or discharged in the older age group. For these reasons models that combine predictors of disease severity and geriatric factors may perform even better than ours, but such models do not exist yet.

In contrast to the prediction rule derived by Meisel *et al.* 'chest pain' as chief complaint was associated with a lower probability of hospital admission in our models for both older and younger patients. This observation could be explained by the care system in the region where the study was performed that patients with ST-elevation myocardial infarction bypass this ED and go to the heart-catheterisation laboratory immediately[22]. Older patients with dyspnoea and syncope also had a decreased chance of hospital admission, which we explain by the fact that those patients with severe dyspnoea or who have not regained consciousness after syncope are triaged 'red' and were excluded from the study.

Although it was one of the important predictors of hospital admission in our models, there were missing values for vital signs in our study database. We believe that these values are missing because the triage nurse probably deemed vital signs registration unnecessary if the patient was not perceived ill. Using missing measurements of vital signs, such as the absence of measured blood pressure, as valuable information in this study, seemed to be a marker of being less ill (table 3). Using the combination of predictors in this study into a prediction model successfully identified the 10% of the ED patient population with the highest risk of hospital admission, for both younger and older patients.

The prediction model for older patients had a lower AUC but higher PPV for this population. When predicting chance of hospital admission, one would want a high positive predictive value. When designing an intervention based on such a prediction model, the patients with the highest risk should be targeted to prevent unnecessary and costly admissions. A low number of false-positives is therefore desirable.

Using the prediction model created in this study identifies the 10% of the ED patient population with the highest probability of hospital admission with a PPV of 71% in the young and 81% in the old.

The PPV for hospital admission was higher in older than in younger patients, likely due to the higher a priori chance of hospital admission for older patients (derivation cohort: 23.1% admission rate in younger patients vs. 43.2% for older patients, validation cohort 24.1% admission rate in younger patients, 44.4% in older patients). In addition, the LR+ was slightly better for older patients, which increases its clinical utility. Thus, this tool could trigger early awareness of the high chance of hospital admission, which could affect the clinical decision-making, preparation for admission, enhancement of ED work flow and shortened length of ED stay.

The overall discriminative performance of the model and odds ratios of the individual predictors were significantly higher for younger patients. This observation could be explained by three different mechanisms. First, the relationship between vital signs and disease severity is likely to be different between younger and older patients. It is well known that with aging the physiology of the body changes, with less homeostatic, respiratory and cardiovascular reserve. In combination with polypharmacy (e.g. beta-blockers), severely ill older patients show less prominent vital sign abnormalities. For example, in this study heart rate was an independent predictor for younger but not older patients. This finding was also shown in two recent studies in which normal vital signs proved to be less specific for the absence of severe illness for older adults[23, 24]. This phenomenon is not captured using standard MEWS-cut off points and could explain a part of the difference in discriminative power between models observed in this study. Second, older patients with multiple comorbidities are often in a delicate equilibrium in which they can still function with relative independence and health. However, relative minor trauma or disease can disturb this equilibrium and result in severe illness and need for hospitalisation[25]. The absence of comorbidities in our model and other or currently existing models, could also explain the difference in the discriminative performance between the models for younger and older patients[10, 11].

Finally, older patients are sometimes hospitalised for their increased vulnerability rather than disease severity. For example, a patient with a small social network and low functional capabilities with the same minor trauma as a younger person, would more easily be hospitalised. It has recently been shown that tools that exclusively use frailty to predict adverse outcomes in older patients, lack specificity and predictive capability[6]. The fact that overall discriminative performance of our model for the older group was lower could be explained by the lack of information about conditions more prevalent among older patients such as impaired cognitive function and functional status.

We therefore hypothesize that the combination of two dimensions: 'disease severity' and 'geriatric phenotypes' such as multi-morbidity and social, cognitive and physical function of the acutely presenting older patient, will result in an optimal model for prediction of adverse events and hospitalisation.

Strengths of this study are the large number of patients and events. These features enable better estimates of test performance parameters of the models. The clear and clinically relevant endpoint also is one of the strengths, as it is without bias whether a patient was admitted or not. The present study had several limitations. First, this was a retrospective study which limits the ability to examine possible predictors which might have been obtained prospectively. There is also risk for information bias, although this was minimized by automatically harvesting data from the electronic patient files. Possible variables were selected based upon earlier research, clinical judgement and availability in the ED records. The second threat was missing measurements of vital

signs, for which we conceived a solution. The fact that a parameter was not measured in a specific patient was considered to contain information with respect to the indication to perform such a measurement and as such analysed alongside measured values rather than imputed. Third, there were no data available on geriatric phenotypes such as multi-morbidity and social, cognitive and physical function, also the comorbidities in young patients are lacking. Whilst these factors could have an important impact on hospitalisation, it was possible to create a robust model with high specificity. Fourth, we used temporal validation to validate the model. Temporal factors could affect who was admitted, for example time of year and changes in admission over time. However, as a sensitivity analysis we performed the same study with a randomly selected split-cohort and found similar results.

Finally, the admission rate in the current single centre study may be different in other care systems which influences its clinical applicability and PPVs of prediction models. While the prediction models has been created according to the recommendations by Stiell *et al.*[26] and has been internally validated using temporal data, it was not prospectively validated, evaluated in another patient population, implemented and disseminated or analysed for cost-effectiveness because it is still in the early stages of development.

In summary, the composition of prediction models for hospital admission are similar for ED patients younger and older than 70-years old, although the AUC is higher in the model for younger patients and the model for older patients showed a higher PPV and LR+. This retrospective study could help identify determinants of admission in older ED patients. Further research should investigate the combination of disease severity with frailty to improve prediction of hospital admission. We are currently performing a multicentre, prospective follow up study (www.apop.eu)[27] in which we will derive, validate and implement a prediction model according to internationally acknowledged recommendations[26] to optimize care for this vulnerable patient group.

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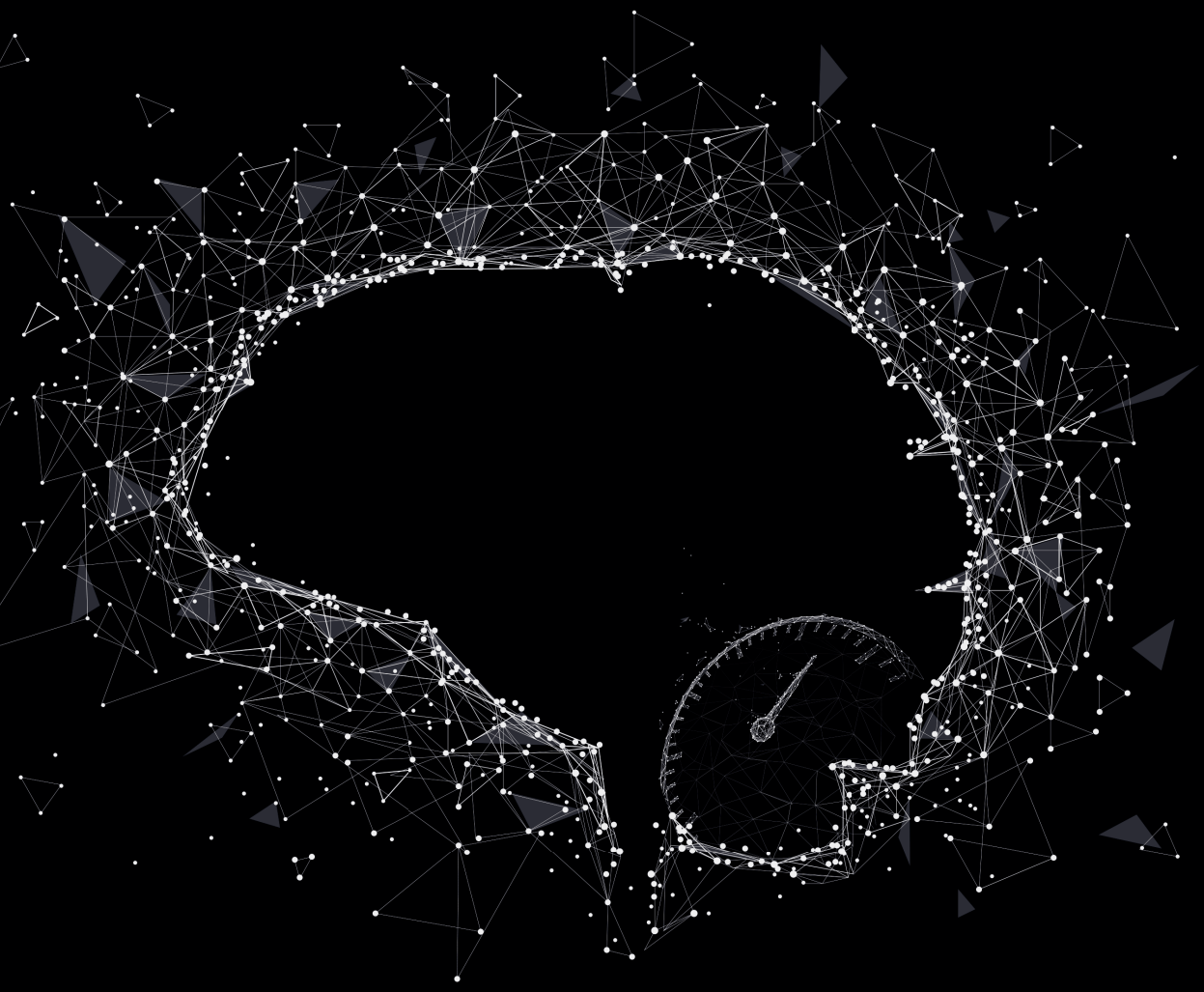

Chapter 6

The APOP-screener to predict functional decline and mortality in older ED patients

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Optimization of the APOP screener to predict functional decline or mortality in older emergency department patients: cross-validation in four prospective cohorts

ABSTRACT

Introduction: Many screening instruments to predict adverse health outcomes in older patients visiting the Emergency Department (ED) have been developed, but successful implementation has been hampered because they are insufficiently validated or not tailored for the intended use of everyday clinical practice. The present study aims to refine and validate an existing screening instrument (the APOP-screener) to predict 90-day functional decline or mortality in older ED patients.

Methods: Consecutive older patients (≥70-years) visiting the EDs of four hospitals were included and prospectively followed. First, an expert panel used predefined criteria to decide which independent predictors (including demographics, illness severity and geriatric parameters) were suitable for refinement of the model predicting functional decline or mortality after 90-days. Second, the model was cross-validated in all four hospitals and predictive performance was assessed. Additionally, a pilot study among triage nurses experiences and clinical usability of the APOP-screener was conducted.

Results: In total 2629 older patients were included, with a median age of 79 years (IQR 74-84). After 90-days 805 patients (30.6%) experienced functional decline or mortality. The refined prediction model included age, gender, way of arrival, need of regular help, need help in bathing/showering, hospitalisation the prior six months and impaired cognition. Calibration was good and cross-validation was successful with a pooled area under the curve of 0.71 (0.69-0.73). In the top 20% patients predicted to be at highest risk in total 58% (95%CI 54%-62%) experienced functional decline or mortality. Triage nurses found the screener well suited for clinical use, with room for improvement.

Conclusion: In conclusion, optimisation of the APOP-screener resulted in a short and more simplified screener, which adequately identifies older ED patients at highest risk for functional decline or mortality. The findings of the pilot study were promising for clinical use.

INTRODUCTION

Up to 45% of all older patients experience functional decline or mortality within three months after an Emergency Department (ED) visit[1]. Multiple screening instruments have been developed to identify older patients at high risk for adverse functional outcomes[2-5]. Although guidelines include the policy to screen all older patients who visit the ED[6], these instruments have been rarely implemented as part of routine care. The frequent rejection of developed screening instruments is likely due to poor external validation or the impossibility to integrate the instrument in daily routine care[7].

The Stiell criteria lists six major methodologic stages to disseminate and implement a developed screener in daily practice[8]. Previously, we have developed and validated the APOP-screener to identify patients at risk of mortality or functional decline[9]. The APOP-screener was more useful to rule-in patients at highest risk, compared to the well-known Identification of Seniors at Risk (ISAR)[9] and other screening instruments[10]. To improve the chance of successful implementation in clinical practice, a refinement process of the screener is advised[8]. In this process accuracy can be improved, the screener can be simplified and acceptance among the people who have to use the screener in daily practice can be evaluated.

In the present study we aimed to optimize the APOP-screener for predicting 90-day functional decline or mortality in older ED patients by selecting predictors based on pre-defined criteria, cross-validation in patients of four hospitals. Additionally, facilitators and barriers of adoption by triage nurses were evaluated in a pilot study.

METHODS

Study design and setting

We conducted a multicentre cohort study among consecutive older patients visiting Emergency Departments (EDs) of four hospitals in the Netherlands: the APOP-study [9]. In short, patients were included from September 2014 – November 2014 in the Leiden University Medical Center (LUMC, Leiden), from March 2015 – June 2015 in Alrijne hospital (Alrijne, Leiderdorp), from May 2016 – July 2016 in Haaglanden Medical Center, location Bronovo (HMC Bronovo, The Hague) and from July 2016 – January 2017 in Erasmus University Medical Center (Erasmus MC, Rotterdam). Training sessions were organized to guarantee that in all hospitals inclusion procedures were equal. During twelve weeks patients were included in the LUMC (7 days a week, 24 hours a day) and in Alrijne hospital (7 days a week, from 10AM-10PM). In HMC Bronovo and Erasmus MC we aimed to include 500 patients. In HMC Bronovo inclusion was performed 6 days a week, from 10AM-10PM and in Erasmus MC 4 days a week (including weekend days) from

10AM-10PM. All patients aged 70-years and over were eligible for inclusion. Exclusion criteria were: red triage category (highest acuity) according to the Manchester Triage System (MTS)[11], an unstable medical condition, no permission of nurse or physician to approach the patient, a language barrier and impossibility to obtain informed consent. The medical ethics committees waived the necessity for formal approval of the study protocol, as the study closely followed routine care. Written informed consent was obtained of all patients or relatives before inclusion.

Baseline

At baseline, data on three domains were assessed. First, demographics including age, sex, living arrangement and level of education. Living arrangement was defined as patients living independent with others, independent alone or in a residential care centre or nursing home. High education includes patients with vocational training or university. Second, severity of medical condition, included arrival by ambulance, fall related ED visits, triage urgency and chief complains as obtained with the Manchester Triage System (MTS), was scored[11]. The 52 possible chief complaints were classified into seven main groups (supplementary table 1 available from https://doi.org/10.1016/j.exger.2018.06.015). Third, the geriatric parameters included the presence of polypharmacy, use of walking device, Katz-ADL (Katz Index of Independence in Activities of Daily Living) score[12] and cognition measured by the Six-Item Cognitive Impairment Test (6-CIT)[13]. Polypharmacy was defined as the use of five or more different medications at home, self-reported by the patient. The Katz-ADL evaluates the ADL situation two weeks prior to the ED visit with six yes/no questions on basic activities of daily living (zero to six point scale). Higher scores indicate more dependency. The 6-CIT is a short cognition test with scores ranging from 0-28, with a score of 11 or higher indicating moderate to severe cognitive impairment, comparable to an MMSE of 24 or lower[14]. All patients with the diagnosis of dementia were classified as positive for cognitive impairment. To reduce the number of questions needed to be asked to test cognition, two questions of the 6-CIT were selected to screen for impaired cognition. Patients were considered cognitively impaired if they incorrectly answered the question 'what year is it now?' and/or 'say the months in reverse order' (incorrect if two or more errors in months). If the patient is diagnosed with dementia or if it is impossible to obtain answers for the two questions for any reason (e.g. due to mental status), cognition was also considered to be impaired.

Outcome

The primary adverse health outcome was the composite outcome of functional decline or mortality at 90-days follow-up, equal to the development study[9]. Mortality was incorporated into the composite outcome, as it can be seen as ultimate decline.

Functional decline was defined as at least one point increase in Katz-ADL score or new institutionalisation (e.g. nursing home admission) at 90-days after ED visit. To obtain follow-up data, patients were contacted by telephone 90-days after the ED index visit. In case of no response after three attempts the general practitioner was contacted to verify phone number and living arrangement (new institutionalisation). Finally, to patients who could not be contacted, a letter was sent with a request for a written response. Data on mortality were obtained from the municipal records.

Refinement of predictors in the model

The original APOP-screener, which predicts 90-day functional decline or mortality and solely 90-day mortality, was developed with data of LUMC patients and validated with Alrijne patients[9]. For refining of the model, instead of redeveloping the APOP-screener with regression techniques, criteria were formulated to select predictors (box1)[15]. Consensus to meet all five criteria of predictors was obtained in a multidisciplinary meeting consisting of physicians (Emergency Medicine, Internal Medicine and Geriatrics), nurses (emergency medicine, internal medicine and geriatrics) and a statistician.

Box 1: Criteria for selection of predictors

Criteria	Explanation
1. Applicable	The collection and definition of predictors should follow routine clinical care as good as possible and require as little extra work as possible
2. Reliably measured	Objective and robust predictor to reduce inter-observer variability or variability between different hospitals.
3. Easily measured	Predictor should be fast and easy to obtain, to ensure screening can be finished in short time.
4. Early available	Predictor should be available at the moment of triage of the patient.
5. Strong predictors	Based on the strength of association with outcome. Based on the prevalence of predictor. A wide distribution is preferred over a narrow distribution.

Cross-validation of the screener

The final selection of predictors represent the APOP-screener and were cross-validated in four hospitals. The LUMC is an academic hospital in with a level 1 trauma centre and Alrijne hospital is a community hospital with a level 2 trauma centre. Both hospitals are located in a small city. The HMC Bronovo hospital is an community hospital with a level 2 trauma centre. The HMC Bronovo hospital is located in a district with relatively many wealthy older people. In the region patients with a suspicion of hip fracture will be sent to the HMC Bronovo. The Erasmus MC is an academic hospital with a level 1 trauma centre and located in the centre of a big city.

Pilot study for usability and acceptance of the screener

Eight triage nurses were instructed to use the refined APOP-screener for one week in patients aged 70 and over to track the time needed to complete the screening and evaluate usability. Afterwards, an evaluation form was sent to the nurses to get an first impression of possible barriers and clinical application of the APOP-screener. A five-level Likert scale was used to score results with the possibility to score strongly disagree (1), disagree (2), neither agree nor disagree (3), agree (4) and strongly agree (5). It was possible to write down additional feedback in free text.

Statistical analysis

Baseline descriptive characteristics are presented as numbers with percentages (%) and median with interquartile range (IQR). Multivariable binary logistic regression was used to estimate the regression coefficients of the prediction model for 90-day functional decline or mortality. Calibration of the prediction model was graphically displayed with calibration plots[16]. A minimum number of 10 events per candidate predictor was used to obtain good predictions with adequate statistical power[15]. Validity of the model was assessed with an internal-external validation design[17]. The robustness of the model was evaluated by a leave-one-hospital-out cross-validation procedure, with patients of each single hospital representing the validation cohort for a model based on the patients of the other three hospitals[18]. External validity was assessed by pooling the cross-validated area under the receiver operating characteristic curves (AUCs) of the four single hospitals using a random-effect meta-analysis[18]. Predictive performance of the model was evaluated for the patients with the highest 30%, 20% and 10% predicted risk, with sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+) and negative likelihood ratio (LR-). Additionally, the prediction model, calibration plot and predictive performance for solely 90-day mortality was assessed. Mean Likert scale scores with standard deviation (SD) were used to analyse usability of the screener. Analysis was performed with IBM SPSS statistics version 23 and R software (version 3.1.1.)

RESULTS

A total of 3544 individual patients aged 70-years and older visited the Emergency Departments (EDs) of the four hospitals combined during the inclusion of the study period. Of those, 3147 were eligible for inclusion in the APOP-study. In total 2629 patients were included (84% of the eligible patients (figure 1)).

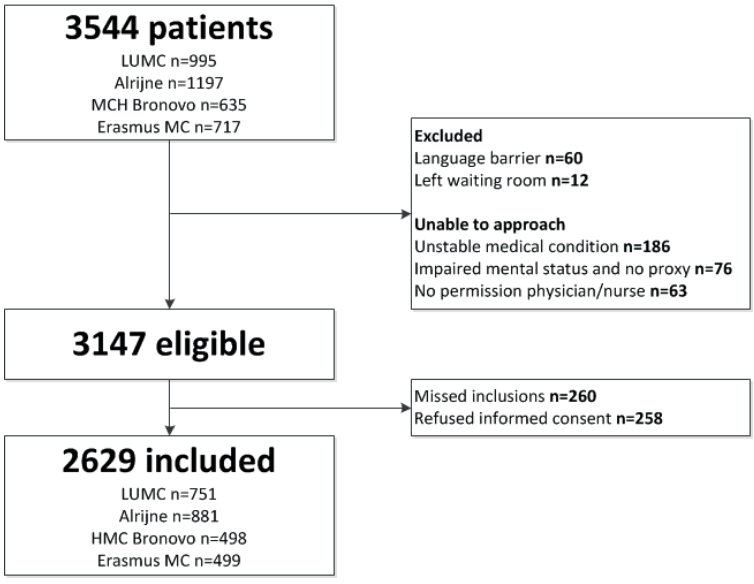

Figure 1: Flowchart of study population

Table 1 shows the baseline characteristics of the APOP-study population and stratified per study centre. The median age was 79 years (IQR 74-84) for the combined group, ranging from a median of 76 years in the Erasmus MC to median 82 years in HMC Bronovo. In total 1236 patients (47.0%) were male, 1339 patients (50.9%) arrived by ambulance and 659 patients (25.1%) experienced a fall prior to the ED visit. Polypharmacy was found in 1552 patients (57.9%). Impaired cognition was present in 492 patients (20.5%).

Refinement of predictors in the model

Table 2 shows the results of the selection of the predictors based on the predefined criteria. The APOP-screener consists of seven predictors which meet all criteria: age, gender, arrival by ambulance, need of regular help (IADL), need for help with bathing or showering, hospitalisation in the prior 6 months and impaired cognition. Arguments of ineligibility of the other predictors can be found in supplementary table 3.

Table 1: Baseline characteristics of older patients visiting the Emergency Department

	All (n=2629)	LUMC (n=751)	Alrijne (n=881)	HMC Bronovo (n=498)	Erasmus MC (n=499)
Demographics					
Age (years), median (IQR)	79 (74-84)	78 (74-83)	80 (75-84)	82 (75-87)	76 (73-80)
Male	1236 (47.0)	362 (48.2)	427 (48.5)	164 (32.9)	283 (56.7)
Living arrangement					
Independent with others	1421 (54.1)	414 (55.1)	498 (56.5)	208 (41.8)	301 (60.4)
Independent alone	991 (37.7)	274 (36.5)	314 (35.6)	231 (46.4)	172 (34.5)
Residential care or nursing home	216 (8.2)	63 (8.4)	69 (7.8)	59 (11.8)	25 (5.0)
High educated	586(22.4)	155 (20.6)	164 (18.6)	147 (29.6)	120 (24.3)
Severity of disease indicators					
Arrival by ambulance	1339 (50.9)	405 (53.9)	432 (49.0)	256 (51.4)	246 (49.3)
Triage urgency					
> 1 hour (green)	717 (27.3)	159 (21.2)	353 (40.1)	104 (20.9)	101 (20.2)
< 1 hour (yellow)	1534 (58.3)	391 (52.1)	470 (53.3)	347 (69.7)	326 (65.3)
< 10 min (orange)	378 (14.4)	201 (26.8)	58 (6.6)	47 (9.4)	72 (14.4)
Chief complaint					
Minor trauma	815 (31.0)	218 (29.0)	232 (26.3)	232 (46.6)	133 (26.7)
Malaise	465 (17.7)	137 (18.2)	176 (20.0)	85 (17.1)	67 (13.4)
Chest pain	393 (14.9)	111 (14.8)	167 (19.0)	57 (11.4)	58 (11.6)
Dyspnoea	320 (12.2)	76 (10.1)	131 (14.9)	43 (8.6)	70 (14.0)
Abdominal pain	282 (10.7)	84 (11.2)	96 (10.9)	35 (7.0)	67 (13.4)
Loss of consciousness	146 (5.6)	49 (6.5)	38 (4.3)	14 (2.8)	45 (9.0)
Others	208 (7.9)	76 (10.1)	41 (4.7)	32 (6.4)	59 (11.8)
Fall prior to ED visit	659 (25.1)	211 (28.1)	192 (21.8)	179 (35.9)	77 (15.4)
Geriatric measurements					
Polypharmacy	1552 (57.9)	441 (58.7)	509 (57.8)	241 (48.4)	331 (66.3)
Use of walking device	1114 (42.5)	302 (40.2)	378 (42.9)	243 (48.9)	191 (38.4)
Katz-ADL, median (IQR)	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-2)	0 (0-1)
Cognitive impairment	492 (20.5)	140 (19.9)	174 (21.6)	111 (23.9)	67 (15.9)

Data are presented as number, percentage unless noted otherwise.

Abbreviations: N: number, IQR: Interquartile range, ADL: activities of daily living, ED: Emergency Department.

Missings; LUMC: 5 level of education, 4 walking device, 6 Katz-ADL, 47 cognitive impairment; Alrijne: 3 level of education, 3 walking device, 22 Katz-ADL, 75 cognitive impairment; Bronovo: HMC Bronovo 2 level of education, 1 walking device, 3 Katz-ADL, 33 cognitive impairment, Erasmus: 1 living arrangement, 6 level of education, 2 walking device, 9 Katz-ADL, 77 cognitive impairment.

Table 2: Selection of predictors for refinement of the APOP-screener

	Applicable	Reliably measured	Easily measured	Readily available	Strong predictor
Age	+	+	+	+	+
Gender	+	+	+	+	+
Living arrangement	-	+	+	+	+
Level of education	+	+	+	+	-
Arrival by ambulance	+	+	+	+	+
Triage category	+	-	+	+	-
Chief complaint	+	-	+	+	+
Fall prior to ED visit	+	-	-	+	+
Vital measurements	+	+	+	-	-
Laboratory results	+	+	+	-	+
Polypharmacy	+	-	-	+	+
Use of walking device	+	+	+	+	-
Need regular help (IADL)	+	+	+	+	+
Need help bathing showering	+	+	+	+	+
Need help dressing	+	+	+	+	-
Hospitalised past 6 months	+	+	+	+	+
Cognitive impairment	+	+	+	+	+

Abbreviations: ED: Emergency Department, IADL: Instrumental activities of daily living.
In bold: eligible predictors.

Cross-validation of the screener

A total of 139 out of 2629 patients (5.3%) were lost to follow-up for data on physical functioning, but from municipal records we verified that they were alive. The incidence of 90-day composite outcome in the study population was 30.6% (805 out of 2629 patients, supplementary figure 1). Table 3 shows the result of the multivariable logistic regression of the refined screener. All selected predictors, except gender, were statistically significant associated with the outcome. The individual predicted risk of a patient to experience the outcome can be calculated by using the equation in the legend of the table or by using a free web-based calculator: http://screener.apop.eu. Cross-validation of the screener was successful, with comparable AUC's between the four individual hospitals (figure 2). External validity of the screener was good, with a pooled AUC of 0.71 (95%CI 0.69-0.73). The predicted probabilities were in line with the observed, as can be seen in the calibration plot (supplementary figure 3). Predictive performance for 90-day functional decline or mortality is shown for the 30%, 20% and 10% patients at highest risk (table 4). Stricter thresholds for high risk increased specificity, positive predictive value (PPV) and positive likelihood ratio (LR+). The PPV for 90-day functional decline or mortality was 0.53 (95%CI 0.49-0.56) in the 30% patients at highest risk, 0.58

(95%CI 0.54-0.62) in the 20% patients at highest risk and 0.60 (95%CI 0.54-0.66) in the 10% patients at highest risk.

Table 3: Prediction model for 90-day functional decline or mortality in older patients visiting the Emergency Department

	OR (95%CI)
Age (per 5 years increase)	1.30 (1.21-1.40)
Male	0.93 (0.78-1.12)
Arrival by ambulance	1.58 (1.32-1.91)
Need help prior to ED visit (IADL)	1.71 (1.39-2.10)
Need help bathing or showering	1.76 (1.40-2.21)
hospitalised past six months	1.54 (1.27-1.87)
Cognitive impairment	1.29 (1.06-1.57)

Abbreviations: OR: odds ratio, ED: Emergency Department, IADL: instrumental activities of daily living.
Equation: 1/(1+exp(-(-5.848 + 0.262 x '(age/5)' + -0.072 x 'male' + 0.460 x 'arrival by ambulance' + 0.534 x 'need help prior to ED visit' + 0.567 x 'need help bathing or showering' + 0.432 x 'hospitalised past six months' + 0.255 x 'cognitive impairment'))).
Application: http://screener.apop.eu/pilot.

Table 4: Predictive performance of final prediction model for 90-day functional decline or mortality

	Number of patients at risk	Sens (95%CI)	Spec (95%CI)	PPV (95%CI)	NPV (95%CI)	LR+ (95%CI)	LR- (95%CI)
30% at highest risk	780	0.52 (0.48-0.55)	0.80 (0.78-0.81)	0.53 (0.79-0.56)	0.79 (0.77-0.81)	2.51 (2.24-2.81)	0.61 (0.57-0.66)
20% at highest risk	521	0.38 (0.35-0.41)	0.88 (0.86-0.89)	0.58 (0.54-0.62)	0.76 (0.74-0.78)	3.15 (2.71-3.67)	0.71 (0.67-0.74)
10% at highest risk	260	0.20 (0.17-0.23)	0.94 (0.93-0.95)	0.60 (0.54-0.66)	0.73 (0.71-0.74)	3.40 (2.69-4.30)	0.85 (0.82-0.88)

Abbreviations: Sens: sensitivity, Spec: specificity, PPV: positive predictive value, NPV: negative predictive value, LR+: positive likelihood ratio, LR-: negative likelihood ratio, CI: confidence interval.

An additional analysis was performed to predict 90-day mortality as a separate end point (supplementary material). In total 9.9% of the patients (259 out of 2629) deceased within 90 days after visiting the Emergency Department (supplementary figure 1). Accuracy of the refined screener was good with an AUC of 0.74 (95%CI 0.71-0.77, supplementary table 3), calibration was successful (supplementary figure 2) and the PPV ranged from 0.20 (95%CI 0.17-0.23) for the 30% patients at highest risk to 0.28 (95%CI 0.23-0.34) for the 10% patients at highest risk (supplementary table 4).

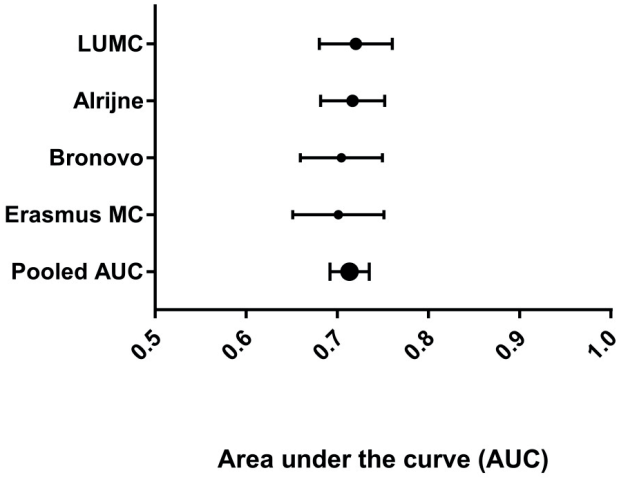

Figure 2: Plot of area under the curve of respective hospitals

Usability and acceptance of the screener in the pilot study

A total of 60 patients was screened by eight triage nurses. The mean time to complete the screener was 93 seconds (SD 29). The overall rating of clinical usability was positive, with a mean Likert score of 3.79 (SD 0.63, supplementary table 5). The screener was easy to administer, the triage nurses found it important to screen and experienced no big burden for the patient. In the current form some nurses experienced an increase in workload. These nurses advised that workload can be reduced by incorporating the APOP-screener in the electronic patient files instead of using the web-based application.

DISCUSSION

The screener was refined by selecting predictors based on predefined criteria for predicting 90-day functional decline or mortality in older Emergency Department patients. The refined model was cross-validated in four hospitals and showed satisfactory discrimination and calibration. Predictive performance was good, with high positive predictive values. A pilot performed by triage nurses showed adequate usability of the screener in clinical practice, with room for improvement.

In the present study the screener was refined in order to increase its usefulness in clinical practice. In a multidisciplinary meeting predictors were chosen with predefined generally accepted criteria[15], which took into account both the association with the outcome and possible barriers for implementation. Compared to the original model, gender and cognition were added and number of medications was removed. Gender is

readily information upon attendance and associated with the outcome[9, 19]. Impaired cognition is highly prevalent in the ED[20, 21], and frequently underdiagnosed[22] and is associated with functional decline[23, 24]. Although number of medications is known to be associated with functional decline and mortality[9], the predictor was not selected for other reasons. Inter observer variability can easily be introduced due to the combined medications of different pharmacological sub classifications or prescribed 'as-needed' and patients tend to hand over pill boxes, which takes too much time at the moment of triage. At the end, the refinement process resulted in a more simplified screener, based on a large heterogenetic group of older patients.

The refined APOP-screener was successful cross-validated in four different hospitals, with universal predictors, independent of the health care system. We therefore assume that the screener is generalisable for EDs in Western countries, but needs to be external validated for confirmation first. Predictive performance of the APOP-screener differs compared to the Identification of Seniors at Risk (ISAR) tool[2] and Triage Risk Screening Tool (TRST)[3]. Sensitivity of the ISAR and TRST are higher (pooled estimate 0.79 and 0.66) and both the specificity (pooled estimate 0.37 and 0.47) and positive likelihood ratio (pooled estimate 1.25 and 1.23) are lower[10]. Although a higher sensitivity will include more patients who will decline, the increased risk to experience the composite outcome for the 'high risk' group by using the screener is minimal. According to these estimates, given the baseline risk of 30% for experiencing the composite outcome, patients with a positive ISAR or TRST screening have a risk of 35% to experience the outcome. We suggest to effectively select patients at highest risk, enabling clinicians to take measures in a smaller group of patients with a higher risk of a potential adverse outcome. The cut-off was therefore set for the 20% patients at highest risk[25]. The risk of experiencing functional decline or mortality in this high risk group increases from 30% (incidence) to 58% (PPV).

Usability of the screener was evaluated among triage nurses in a pilot. With a mean time of 93 seconds to complete screening, the APOP-screener is now shorter compared to the original screener. Although the screener was easy to administer and no burden for the patient, suggestions for improvement were given. Some triage nurses experienced difficulties in obtaining the screening result via the web-based application. To make the screener more applicable for routine care, the screener needs to be integrated in the electronic patient files. Second, no follow-up interventions were conducted after screening yet, which ensures that some nurses experienced that workload rather increased than decreased. As an example, in order to reduce the ED length of stay, a fast-track admission trajectory can be developed in high risk patients who need to be hospitalised. We are currently developing a concomitant educational program to train medical personal and will take the feedback into account.

The APOP-screener has been prospectively validated[9] and in the present study the screener is successfully refined to increase its usefulness in clinical practice while preserving predictive performance. The next step is to implement the APOP-screener in clinical practice. In addition, an implementation study will be conducted to translate the research into clinical practice and to achieve acceptance of the screener of involved stakeholders. At the same moment the educational program will be disseminated to increase awareness of all health care professionals, of which low-risk patients also will benefit. In patients at high risk for functional decline or mortality and in patients with cognitive impairment follow-up actions and interventions will be conducted (box 2). After patient and physicians acceptance is evaluated, the balance between 'costs' and 'benefits'[26] will be investigated and a strategy for wide-spread dissemination and implementation will be developed.

Box 2: Overview of possible actions and interventions after screening result

	High risk functional decline or mortality	**Cognitive impairment**
Emergency department		
(triage) Nurse	- Informs involved health care professionals - If patient is alone, ask family member or care giver to come to the ED. - Nurses patient on a comfortable bed	- Informs involved health care professionals - If patient is alone, ask family member or care giver to come to the ED - Nurses patient on a comfortable bed - Starts multicomponent delirium prevention measures
(ED) Physician	Takes the screening result into account in the diagnostic process (e.g. screen for delirium) and decision making.	
Patients discharged home		
(triage) Nurse	- Put patient on the list to call back the next day to verify status and to answer questions	- Put patient on the list to call back the next day to verify status and to answer questions
(ED) Physician	- Informs general practitioner (by telephone or email)	- Hands over paper discharge instructions - Informs general practitioner (by telephone or email)
Patients admitted to the hospital		
(triage) Nurse	- Informs colleague - Invites family member or care giver to stay with the patient during transfer	- Informs colleague - Invites family member or care giver to stay with the patient during transfer
(ED) Physician	- Informs colleague - Ask geriatric liaison service in consultation	- Informs colleague - Ask geriatric liaison service in consultation

Some limitations have to be addressed. First, we were not able to investigate all potentially important determinants of the composite outcome (e.g. malnutrition or the presence of care givers). Second, the screener needs further validation to obtain performance in other countries. Third, the pilot study has insufficient power to draw firm conclusions and did not test the effect of applying measures in high-risk patients. Currently we are conducting a large implementation study of the refined APOP-screener. Our study has several strengths. First, a large unselected group of older patients visiting the ED of four hospitals was included (84%) with a high follow-up rate (95%). Second, the prospective design of the study enabled to take important geriatric parameters, such as cognition, into account. Third, the internal-external validation design enabled to use as much possible data to increase generalisability of the screener.

In conclusion, optimisation of the APOP-screener resulted in a short and more simplified screener, which adequately identifies older ED patients at highest risk for functional decline or mortality. The findings of the pilot study were promising for clinical use.

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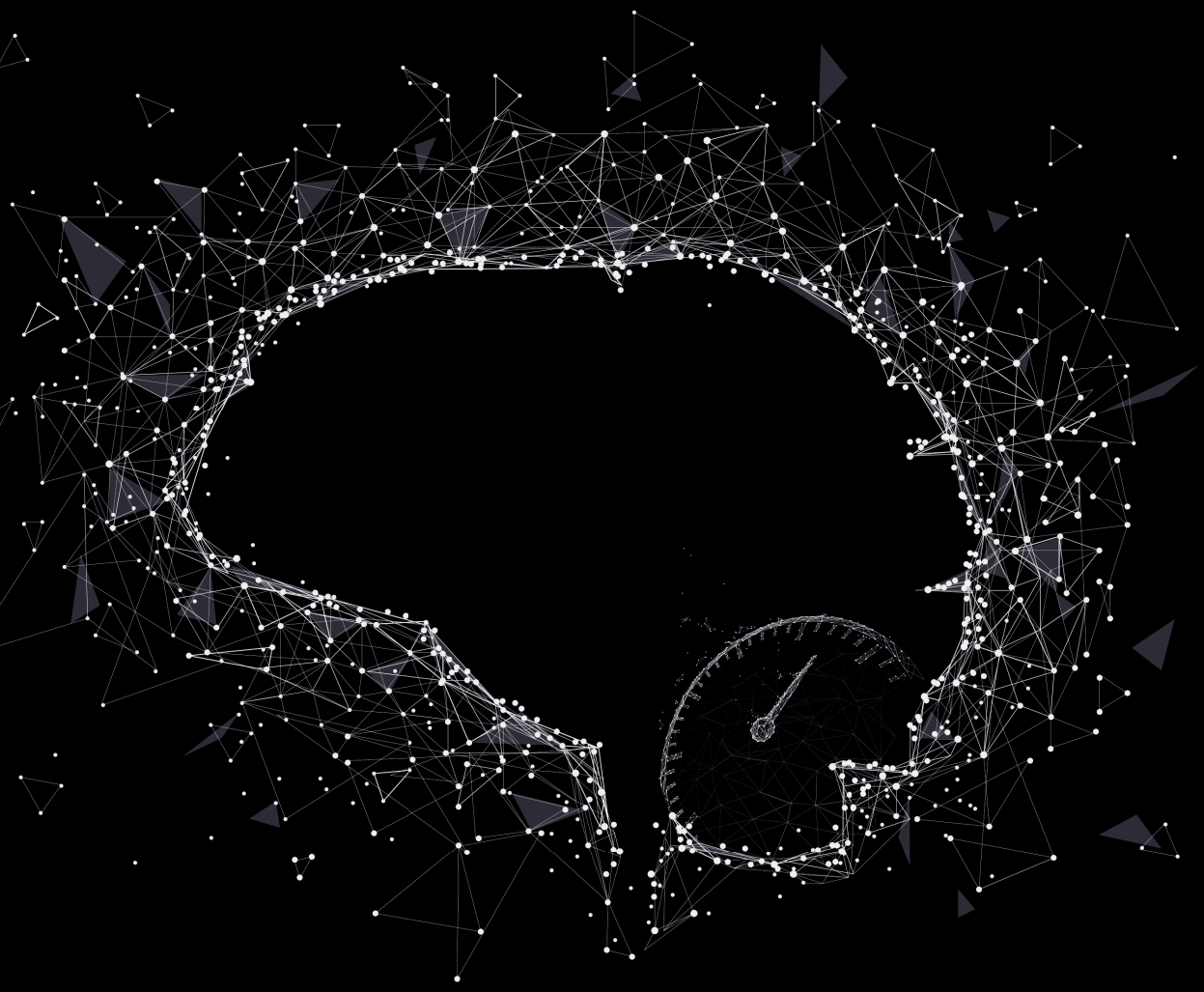

Chapter 7

Early delirium screening in older ED patients

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CAM-ICU may not be the optimal screening tool for early delirium screening in older Emergency Department patients, a prospective cohort study

ABSTRACT

Background: Delirium is a frequent problem among older patients in the Emergency Department (ED) and early detection is important to prevent its associated adverse outcomes. Several screening tools for delirium have been proposed for the ED, such as the Confusion Assessment Method-Intensive Care Unit (CAM-ICU). Previous validation of this tool for use in the ED showed varying results, possibly because they were administered at different or unknown time points.

Objective: To study incidence of delirium in older (≥70-years) ED patients using the CAM-ICU.

Design: Prospective cohort study, taking place in one tertiary care and one secondary care hospital in the Netherlands.

Methods: All patients aged 70-years and older attending the ED were included. We screened for delirium within 1 hour after ED registration using the CAM-ICU performed by trained medical students. We assessed the number of positive CAM-ICU scores. For comparison we determined the Six-Item Cognitive Impairment Test (6-CIT), using a cut-off point of ≥14 points indicating possible delirium, which has previously associated with the presence of delirium using gold standard assessment.

Results: A total of 997 patients were included in the study, with a median age of 78 years (interquartile range 74-84). Delirium as assessed with CAM-ICU was positive in only 13 (1.3%) patients. 95 (9.5%) patients had 6-CIT ≥14.

Conclusion: We found a delirium incidence of 1.3% using the CAM-ICU, which was much lower than the expected incidence of around 10% as been frequently reported in literature and what we find when using the 6-CIT. This low incidence may be explained the early application of the test, lack of observation time or lack of information from family members. The CAM-ICU seems inappropriate for early screening in the ED.

INTRODUCTION

Delirium is highly prevalent in older Emergency Department patients (ED)[1, 2], but is frequently missed[3, 4]. It is important to detect delirium[5, 6] at an early stage because then the associated adverse outcomes may be prevented by[7] protective measures.
Early detection of delirium by a complete, but time consuming assessment by a psychiatrist or geriatrician is not feasible in clinical ED practise. Therefore, several screening tools to detect delirium in the ED have been investigated, such as the Confusion Assessment Method-Intensive Care Unit (CAM-ICU[8]). In two recent studies, the CAM-ICU has been validated for ED use, by comparing it with a gold standard, i.e. assessment by a psychiatrist using the DSM-IV. Van de Meeberg *et al.*[1] investigated the CAM-ICU in the ED setting in the Netherlands and showed a 100% sensitivity and 98% specificity. However this was in discrepancy with a study by Han *et al.*[8] in which the performance of this tool was modest with a sensitivity of 72%.
This difference in sensitivity might be explained by a difference when the tool was performed by different care givers or because it was used at different time points.
The goal of this study was therefore to investigate the incidence of delirium in two EDs in the Netherlands by using the CAM-ICU in clinical practice, performed at an early stage during de ED visit.

METHODS

Study design and setting

This was a prospective multicentre cohort study of which a detailed description has been published previously[9]. For the analysis in this manuscript, data of two hospitals were used as CAM-ICU score was only available in these hospitals. One tertiary care hospital (Erasmus University Medical Center, Erasmus MC, Rotterdam) and one secondary care hospital (Haaglanden Medical Center, location Bronovo, HMC Bronovo, The Hague). During 3 month periods (years 2016/2017) Emergency Department patients aged 70-years and older were included in this study.

Selection of participants

All patients were included consecutively. Patients were included between 10AM and 10PM, 6 days a week in the HMC Bronovo and 4 days a week in the Erasmus MC. Patients with an unstable medical condition, those with a disturbed mental status without an available proxy to provide informed consent and those who did not speak English or Dutch were excluded. Written informed consent was obtained in all participants. The medical ethics committee of both hospitals approved the study.

Methods and measurements

Within 1 hour of arrival to the ED patients were included and a short battery of tests was performed by a selected group of trained medical students.

Delirium was measured using the Confusion Assessment Method-Intensive Care Unit (CAM-ICU)[10]. This is a 4-step assessment method with items on altered mental status or fluctuating course, inattention and altered level of consciousness or disorganized thinking. This test has been previously studied in Emergency Department settings[1, 8].

The Six-Item Cognitive Impairment Test (6-CIT) was used to measure both cognition and delirium[11]. This short 2-3 minute test consist of items on memory, orientation and attention. Patients with a 6-CIT score of ≥11, those with self-reported dementia and those unable to perform the 6-CIT were categorized as having cognitive impairment. In a recent study[2] a cut-off score of 6-CIT ≥14 was validated for delirium with expert diagnosis of a geriatrician using DSM-V criteria.

Outcome

The main outcome of this study was the incidence of delirium, defined as a positive CAM-ICU. This was compared with the incidence of 6-CIT ≥14 points.

Statistical analysis

Baseline characteristics and incidence data are presented as mean with standard deviation (SD) in case of normal distribution or as median with interquartile range (IQR) in case of skewed distribution or as numbers with percentages (%). Whether the incidence of delirium measured using the two different tests was significantly different, McNemars test was used. Statistical analyses were performed using IBM SPSS statistics package (version 23).

Declaration of sources of funding

This work was supported by the Netherlands Organisation for Health Research and Development (grant number 627004001). The sponsor had no role in the design of the study, methods, study recruitment, collection or analysis of the data and had no role in the preparation of the paper.

RESULTS

A total of 1460 patients visited the Emergency Departments of both hospitals during the study period, of which 1182 patients were eligible for inclusion. The 997 included patients represent 84.3% of the eligible patients during the inclusion hours (figure 1).

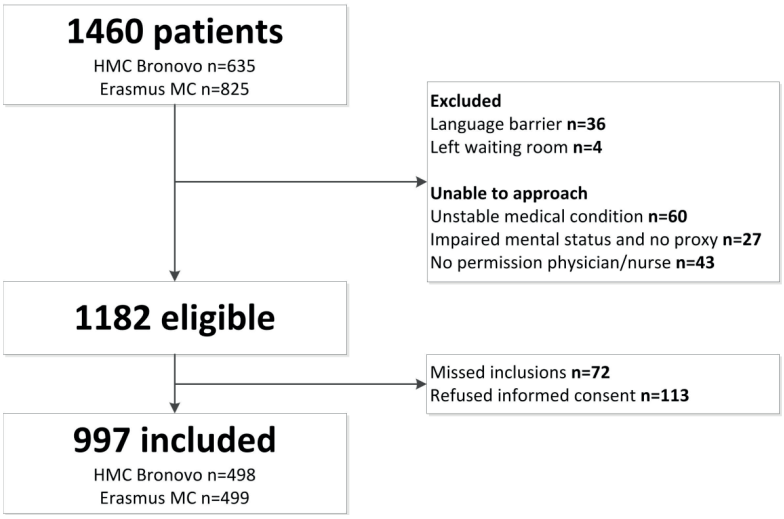

Figure 1: Flowchart of patient inclusion

Patient characteristics

As shown in table 1 the median age was 78 years (IQR 74-84) and 447 patients (44.8%) were male. A total of 267 patients (27.0%) received high education and 84 (8.4%) lived in a residential care or nursing home. Approximately half of the patients (n=502, 50.4%) arrived by ambulance, with a most patients needing help within one hour (n=673, 67.5%). The median number of medications used was 5 (IQR 3-8) and most people were independent in ADL function (Katz-ADL median 0, IQR 0-1).

Delirium

The CAM-ICU was performed in 960 patients, of which only 13 patients scored positive (1.3%) as can be seen in table 2. Of patients with positive CAM-ICU, five were previously diagnosed with dementia, five had cognitive impairment (6-CIT ≥11) and three were unable to perform the 6-CIT test due to confusion. For comparison, 95 (9.5%) patients had a 6-CIT of ≥14 points. The difference between the incidence as measured with these two tests was statistically significant ($p<0.001$). As a sensitivity analysis patients with self-reported dementia were excluded, this showed similar results. Three hundred patients (30.0%) suffered from cognitive impairment in this cohort.

Table 1: Baseline characteristics of study population

Characteristics	All patients n=997
Demographics	
Age (years), median (IQR)	78 (74-84)
Male	447 (44.8)
High education	267 (27.0)
Living in a residential care/nursing home	84 (8.4)
Hospital	
HMC Bronovo	498 (49.9)
Erasmus MC	499 (50.1)
ED presentation characteristics	
Arrival by ambulance	502 (50.4)
Triage urgency	
> 1 hour	205 (20.6)
< 1 hour	673 (67.5)
< 10 minutes	119 (11.9)
Fall related ED visit	256 (25.7)
Main complaint	
Minor trauma	365 (26.6)
Malaise	152 (15.2)
Chest pain	115 (11.5)
Dyspnea	113 (11.3)
Abdominal pain	102 (10.2)
Other	91 (9.1)
Syncope	59 (5.9)
Geriatric characteristics	
Hours of home-care, median (IQR)	0 (0-3)
Use of walking device	434 (43.7)
Number of medications, median (IQR)	5 (3-8)
Katz-ADL, median (IQR)[3]	0 (0-1)

Data are presented as number, percentage unless noted otherwise.
Abbreviations: n: number, IQR: interquartile range, ED: Emergency Department
Data is complete, except for use of walking device (n=3 missings), living in residential care home (n=1 missings), level of education (n=8 missings), Katz-ADL (n=12 missings), hours of home care (n=12 missings).

Table 2: Incidence of delirium measured using the CAM-ICU

	Total n=997
Delirium - Positive CAM-ICU	**13 (1.3)**
Q1. Acute change/fluctuating course[a]	118 (12.3)
Q2. Inattention[b]	24 (2.4)
Q3. Altered level of consiousness[c]	13 (1.3)
Q4. Disorganized thinking[d]	2 (0.2)

Abbreviations: CAM-ICU: Confusion Assessment Method -Intensive Care Unit, Q: question.
[a]Number of measured values n=960 (missing from total n=37), [b] Number of measured values 106 (missing from previous question n=12), [c]Number of measured values n=19 (missing from previous question n=5), [d]Number of measured values n=2.

DISCUSSION

The main finding of this study is that the incidence of delirium, as assessed by the CAM-ICU, was only 1.3% when performed early after ED arrival. 9.5% of patients had a 6-CIT score of ≥14 points, which is comparable with delirium incidence as reported in literature.

This study is in strong contrast with a previous study by Van de Meeberg *et al.*[1]. In this study, the CAM-ICU was implemented in the ED and compared to a subsample of patients in which delirium was independently evaluated using the DSM-IV criteria. It showed a sensitivity of 100% and specificity of 98%. In this study CAM-ICU was performed by ED nurses, doctors or the study investigator at an unknown time after ED arrival. The subsample of patients which was used to validate the CAM-ICU was selected which could have led to verification bias.

Han *et al.*[8] performed a study in which the CAM-ICU was compared to a reference standard of a psychiatrist assessment in all patients. These assessments were conducted within 3 hours. Both research assistants and doctors performed the CAM-ICU. Sensitivity of the research assistants to detect delirium was 68%, that of the doctors was 72%, both had a specificity of 98.6%.

The differences between raters as shown by Han *et al.* might have influenced our results, as we used trained medical students to perform the test.

In addition, the test in our study was performed sooner (<1 hour of ED arrival), possibly making this test less reliable as this decreases observation time. This might be relevant because answering the first question of the CAM-ICU needs either observation time or informant history, the latter of which is only available in 50% of older ED patients[2]. The discrepancy between the incidence of a positive CAM-ICU and 6-CIT ≥14 may be explained by the fact that the 6-CIT contains no items needing informant history or

observation time. The incidence of a 6-CIT ≥14 approximated the ED delirium incidence reported in the literature[4, 5, 12, 13].

We propose that rather than focussing solely on delirium and using the CAM-ICU, cognition should be tested using a reliable tool at an early stage of ED visit to get patients with possible delirium or risk of delirium (i.e. cognitive impairment) into the physicians scope. Several tools which test for both delirium and cognitive impairment exist, such as the 6-CIT or 4-AT. Differentiating between delirium and previously existing impaired cognition can be difficult and it has been recently proposed that making the distinction is not needed in the ED, as patients should be treated on a 'need of care' basis[14].

This study has several weaknesses, first we did not perform a gold standard assessment of delirium using a clinical judgement by a psychiatrist or geriatrician. Second, we trained the medical students to perform the tests, but it could be argued that these students may have fewer clinical knowledge or observational skills than trained doctors or nurses. The students were not observed and we did not perform inter-rater reliability measures. However, when using the 6-CIT we found an incidence that approximates current literature. A major strength of the study is the large sample size of nearly 1000 patients and the unselected patient group.

To conclude, delirium as assessed by CAM-ICU, early after arrival to the Emergency Department leads to a unexpectedly low incidence. The CAM-ICU might not be an appropriate screening tool to detect delirium at an early stage in the ED.

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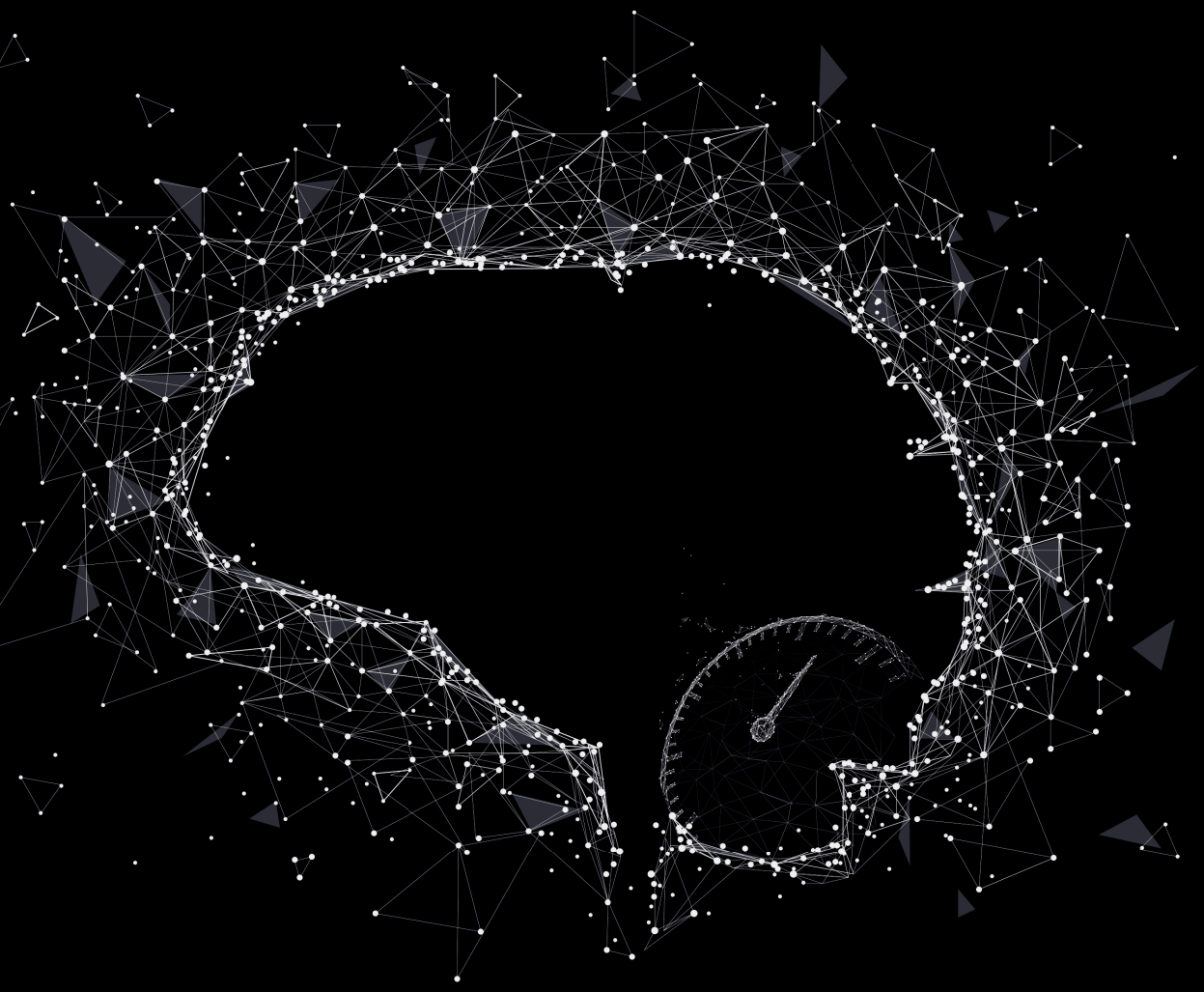

Chapter 8

Vital signs and impaired cognition in older ED patients

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Vital signs and impaired cognition in older Emergency Department patients: the APOP-study

ABSTRACT

Background/objectives: Cognitive impairment is a frequent problem among older patients attending the Emergency Department (ED) and can be the result of pre-existing cognitive impairment, delirium, or neurologic disorders. Another cause can also be acute disturbance of brain perfusion and oxygenation, which may be reversed by optimal resuscitation. The aim was to assess the relationship between vital signs, as a measure of acute hemodynamic changes, and cognitive impairment in older ED patients.

Design: Prospective cohort study.

Setting: EDs of two tertiary care and two secondary care hospitals in the Netherlands.

Participants: 2629 patients aged 70-years and older.

Measurements: Vital signs were measured at the moment of ED arrival as part of routine clinical care. Cognition was measured using the Six-Item Cognitive Impairment Test (6-CIT).

Results: The median age of patients was 78 years (IQR 74-84). Cognitive impairment was present in 738 patients (28.1%). When comparing lowest with highest quartiles, a systolic blood pressure of <129 mmHg (OR 1.37, 95% confidence interval (95%CI) 1.05-1.77), a diastolic blood pressure of <68mmHg (OR 1.32, 95%CI 1.02-1.71) as well as a mean arterial pressure of <90mmHg (OR 1.33, 95%CI 1.03-1.73) were associated with increased risk of cognitive impairment. A higher respiratory rate (>21/min) was associated with increased risk of impaired cognition (OR 2.07 (95%CI 1.55-2.77) as well as oxygen saturation of <95% (OR 1.63, 95%CI 1.25-2.13).

Conclusion: Abnormal vital signs that associate with decreased brain perfusion and oxygenation also associate with cognitive impairment in older ED patients. Although this may partially reflect the association of disease severity with delirium, impaired cognition may also be caused by acute disturbance of brain perfusion and oxygenation. More research is needed to establish whether intervening and improving these vital signs will also acutely improve cognition.

INTRODUCTION

Impaired cognition is a frequent problem among older patients in the Emergency Department (ED)[1, 2]. The incidence of cognitive impairment in older ED patients is approximately 30%[3-7] and is independently associated with adverse outcome[3]. ED delirium incidence rates of approximately 10% have been reported[8-14] and dementia was found in 3-15% of older ED patients[15-17]. Cognitive impairment in the ED can reflect pre-existing cognitive disturbance or disease (amongst which dementia), delirium and neurological disorders like encephalopathy. Alternatively, acute disturbance of brain perfusion and oxygenation due to acute hemodynamic changes or a combination of these factors may also cause acute cognitive impairment. A portion of older ED patients may suffer from possibly reversible cognitive impairment due to compromised circulation to the brain. If there is a connection between impaired brain perfusion and oxygenation due to acute hemodynamic changes and cognitive impairment in the older patients this may be a first step into investigating reversibility by optimal resuscitation in more depth.

The relationship between hemodynamic status and cognitive impairment has been investigated before[18]. There appears to be a close link between cardiac function on the one hand and cognitive functioning on the other. Changes in cerebral blood flow cause chronic alterations to the brain, but at least some of these alterations are reversible when blood flow is restored. In patients with chronic heart failure, cognitive function improved when cardiac function improved and in patients with carotid occlusion there was a causal relationship between reduced cerebral blood flow and impaired cognition[18]. In the latter case it was proposed that cognitive impairment was caused by potentially reversible lactate accumulation in the brain[19]. But also decreased pulsatility of arterial blood flow, limited autoregulation of cerebral blood flow and chemoregulation by PaCO2 and pH could have influence[18, 20]. To our knowledge, it has never been established whether there is an association between hemodynamics and cognition specifically in acutely ill older patients.

We therefore performed a multicentre prospective cohort study in which we aimed to investigate the relationship between vital signs, as a measure for acute hemodynamic changes, and cognitive impairment in over 2500 older ED patients.

METHODS

Study design and setting

This was a prospective multicentre cohort study which was performed in two tertiary care and two secondary care hospitals in the Netherlands. Older patients visiting the ED

of these participating hospitals were included in this study. A detailed description has been published elsewhere[21]. In short, patients were included from September 2014 – November 2014 in the Leiden University Medical Center (LUMC, Leiden), from March 2015 – June 2015 in Alrijne hospital (Alrijne, Leiderdorp), from May 2016 – July 2016 in Haaglanden Medical Center, location Bronovo (HMC Bronovo, The Hague) and from July 2016 – January 2017 in Erasmus University Medical Center (Erasmus MC, Rotterdam). Patients were included 24/7 in the LUMC hospital, 7 days a week (from 10AM-10PM) in Alrijne Hospital, 6 days a week (from 10AM -10PM) in the HMC Bronovo and 4 days a week (from 10AM-10PM) in Erasmus MC.

Selection of participants

All patients aged 70-years and older were included consecutively. Patients who were triaged for a need of immediate care (Manchester Triage category Red), patients with an unstable medical condition, due to denied permission of the nurse or physician to enter the room and patients with a disturbed mental status without a proxy to provide informed consent were excluded. Also patients with a language barrier were not eligible. Patients could only be included in the study once, even if they had multiple ED visits during the study period. Two patients groups bypassed the ED and were therefore impossible to include; patients with a ST-elevation myocardial infarction were directly sent to the catheterization room; and patients with stroke and eligible for thrombolytic therapy were directly sent to the neurology ward. Written informed consent was obtained from all participants before inclusion. The medical ethics committee of the four hospitals approved the study.

Methods and measurements

Teams of trained medical students included patients within 1 hour after arrival to the ED. The data collectors conducted a short 5-10 minute questionnaire on a tablet computer after which data was immediately sent to a secured database. Additional information was gathered from patient files in a standardized manner and assessed for quality by JdG.

At baseline, data on three domains were assessed: demographics, disease severity, and geriatric measurements. Demographics consisted of age, gender, living arrangement and level of education. Severity of disease consisted of characteristics related to the ED visit: way of arrival, triage category by Manchester Triage System (MTS)[22], main complaint, fall related ED visit and vital signs. Geriatric measurements consisted of: the number of different medications stated by the patient, history of diagnosed dementia reported by patient or proxy, current use of a walking device, hours of home-care provided by a professional organisation and the Katz Index of Independence in Activities of Daily Living (Katz-ADL)[23] questionnaire. MTS category was divided into three groups,

very urgent (needing treatment within 10 minutes), semi-urgent (needing treatment within 1 hour) and non-urgent (treatment can be delayed until after 1 hour).
Cognition was measured using the Six-Item Cognitive impairment Test (6-CIT). This short 2-3 minute test contains items on orientation, memory and concentration and has been validated[24] and used before in ED settings[17]. Scoring ranges from 0-28, with higher scores indicating more cognitive impairment. Patients with a 6-CIT score of 10 points or lower were considered to have normal cognition, those with 6-CIT ≥11 were categorized as 'cognitive impairment'. Also patients with pre-existing dementia and those who were unable to perform the cognition test were classified as 'impaired cognition'.
For the vital signs measurements the first set of reliable vital signs measurement was taken from the electronic medical records. 92% of all vital signs were measured within the first 15 minutes of ED arrival, 98% were measured within the first 30 minutes. Automated measured vital signs were: systolic and diastolic blood pressure (in millimetres of mercury, mmHg), heart rate (per minute), oxygen saturation (in percentage). Respiratory rate was measured automatically in LUMC and Alrijne Hospital. Respiratory rate and capillary refill time were measured by hand by the data collectors in the HMC Bronovo and Erasmus MC. Temperature was measured using a tympanic thermometer and manually registered in the electronic medical record by the nurse.
Laboratory test results were extracted from the electronic medical records. The first measurement during the ED visit was registered. Biochemical measures that may reflect perfusion or are essential for oxygen delivery were assessed[25]: creatinine was measured in µmol/liter, urea was measured in mmol/liter and haemoglobin in mmol/liter.

Outcome

The main outcome of this study was cognitive impairment, defined as a 6-CIT of 11 points or higher, pre-existing dementia or the inability to perform the cognition test.

Analysis

Patient characteristics are presented as mean with standard deviation (SD) in case of normal distribution, median with interquartile range (IQR) in case of skewed distribution or as numbers with percentages (%). Vital signs and laboratory test results (creatinine, urea, haemoglobin) were divided into quartiles. Using logistic regression the odds ratio (OR) and 95% confidence interval (95%CI) for cognitive impairment was calculated per quartile. To assess whether there was an association between vital sign quartile and cognitive impairment, the p-value for trend between quartiles was calculated using logistic regression. The level of significance was set at $p<0.05$. Statistical analyses were performed using IBM SPSS Statistics package (version 23).

Sensitivity analysis

In a sensitivity analysis a similar analysis was performed excluding patients with pre-existing dementia or inability to perform the cognition test. Also patients with minor trauma (such as isolated extremity injuries, wounds and minor falls) were excluded for this analysis, since no severe acute hemodynamic changes were expected in this patient group.

As a second sensitivity analysis cognition was divided into six categories: normal cognition, mild cognitive impairment (6-CIT 8-10), cognitive impairment (6-CIT 11-13), severe cognitive impairment (6-CIT ≥14), missing 6-CIT and pre-existing dementia. Mean vital signs were calculated for these different categories and p-value for trend was assessed among the first four categories using linear regression.

In supplemental table S1 data on association between pulse pressure and impaired cognition is additionally shown (availabe upon request).

RESULTS

A total of 3544 patients visited the ED of the participating hospitals during the study period, of which 3147 patients were eligible for inclusion (figure 1), 2629 patients were included which was 83.5% of all eligible patients.

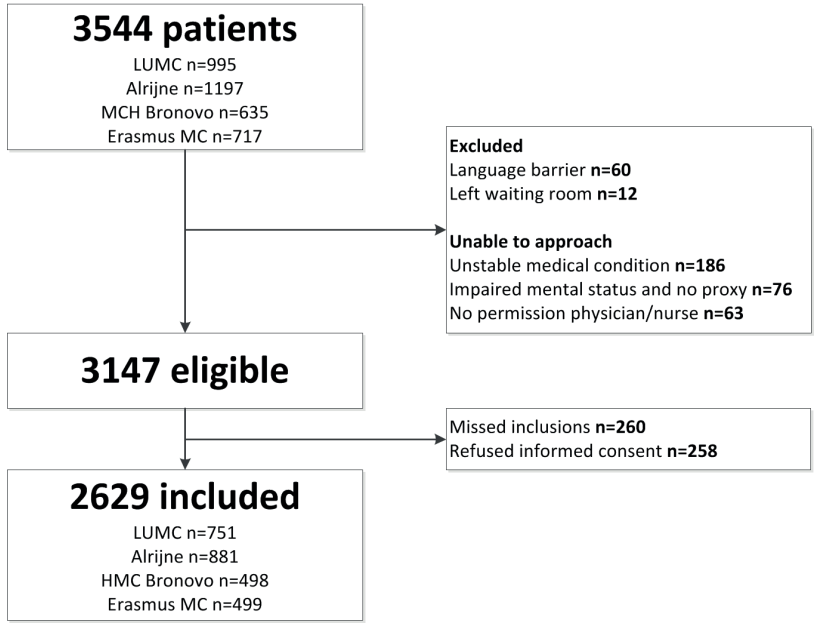

Figure 1: Flowchart of study population

Baseline characteristics

Table 1 shows the baseline characteristics of the study population. Median age of participants was 79 years (interquartile range (IQR) 74-84) and approximately half of them was male (n=1236, 47.0%). A minority of patients received high education (n=5869, 22.4%) and only a small percentage lived in a nursing home (n=216, 8.2%). The majority of patients arrived by ambulance (n=1339, 50.9%) and most had a problem needing medical attention within 1 hour (n=1534, 58.3%). Mean vital signs of the study population were a systolic blood pressure of 149 mmHg (SD 28), mean heart rate of 84/min (SD 22) and respiratory rate of 19/min (SD 6). The participants in this study were living relatively independent, with a median of 0 hours of home care per week (IQR 0-3 hours) and a median Katz-ADL of 0 (IQR 0-1). Cognitive impairment was found in 738 patients (28.1%).

Association of vital signs with impaired cognition

Systolic blood pressure was associated with increased risk of impaired cognition with an OR of 1.37 (95%CI 1.05-1.77) when comparing the lowest with the highest quartile of this vital sign, as can be seen in figure 2 and supplemental table S1. A lower diastolic blood pressure (OR 1.32, 95%CI 1.02-1.71) and mean arterial pressure (OR 1.33, 95%CI 1.03-1.73) were also associated with impaired cognition.

Furthermore, respiratory rate associated with a higher risk of impaired cognition in older ED patients (OR 2.07, 95%CI 1.55-2.77). Finally, oxygen saturation (OR 1.63, 95%CI 1.25-2.13) associated with impaired cognition when comparing the quartile with the lowest oxygen saturation of approximately 93% with the highest quartile (oxygen saturation range 99-100%). Heart rate, pulse pressure, capillary refill and temperature were not associated with increased risk of cognitive impairment.

Table 1: Patients characteristics of study population

Characteristics	**n=2629**
Demographics	
Age (years), median (IQR)	79 (74-84)
Male, n (%)	1236 (47.0)
High education, n (%)	586 (22.4)
Living in a residential care/nursing home, n (%)	216 (8.2)
Hospital, n (%)	
LUMC	751 (28.6)
Alrijne	881 (33.5)
HMC Bronovo	498 (18.9)
Erasmus MC	499 (19.0)

Table 1: Patients characteristics of study population (*continued*)

Demographics	n=2629
ED presentation characteristics	
Arrival by ambulance, n(%)	1339 (50.9)
Triage urgency, n (%)	
> 1 hour	717 (27.3)
< 1 hour	1534 (58.3)
< 10 minutes	378 (14.4)
Fall related ED visit, n (%)	659 (25.1)
Main complaint, n(%)	
Minor	815 (31.0)
Malaise	465 (17.7)
Chest pain	393 (14.9)
Dyspnea	320 (12.2)
Abdominal pain	282 (10.7)
Other	208 (7.9)
Syncope	146 (5.6)
Vital signs	
Systolic BP, mmHg	149 (28)
Diastolic BP, mmHg	79 (17)
Mean Arterial Pressure, mmHg	102 (18)
Heart rate/min	84 (22)
Respiratory rate/min	19 (6)
Oxygen saturation, median (IQR)	97 (95-98)
Temperature, ^{0}C	36.9 (0.9)
Capillary refill, sec, median (IQR)	2 (2-3)
Geriatric characteristics	
Hours of home-care, median (IQR)	0 (0-3)
Use of walking device, n (%)	1114 (42.5)
Number of medications, median (IQR)	5 (3-8)
Katz-ADL, median (IQR)	0 (0-1)
Cognitive impairment, n (%)	738 (28.1)

Data is presented as mean, SD unless noted otherwise.
Abbreviations: n: number, %: percentage, IQR: interquartile range, ED: Emergency Department, 6-CIT: Six-Item Cognitive Impairment Test, Katz-ADL: Katz Index of Independence in Activities of Daily Living BP: blood pressure, mmHg: millimetres of mercury, min: minute, ^{0}C: degrees Celsius, sec: seconds.
Missing values: hours of home care (n=72), Katz-ADL baseline (n=40), level of education (n=16), living in nursing home (n=1), use of walking device (n=10), systolic BP (n=375), diastolic BP (n=379), mean arterial pressure (n=379), heart rate (n=405), respiratory rate (n=861), oxygen saturation (n=438), temperature (n=716), capillary refill (n=1705).

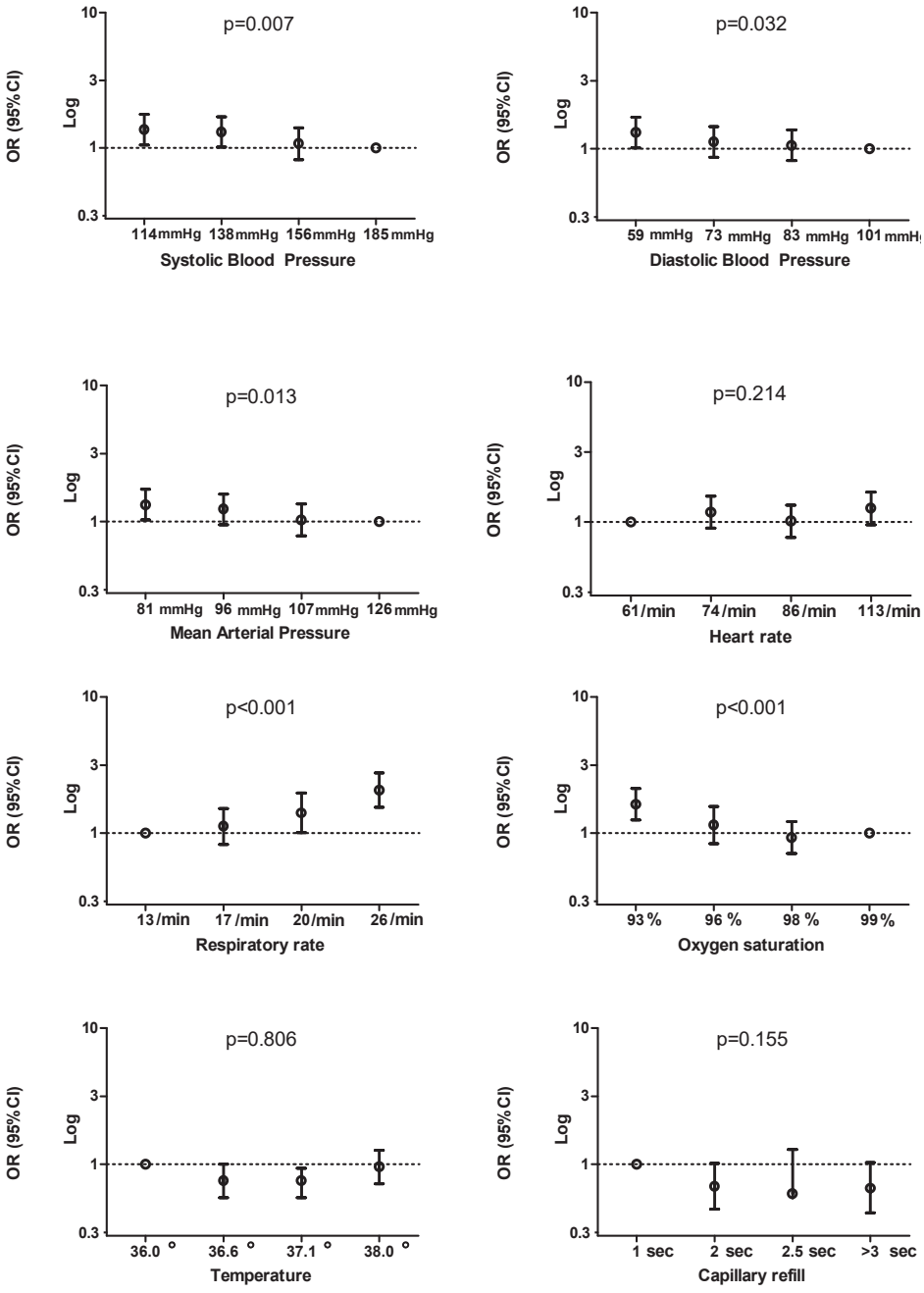

Figure 2: Quartiles of vital signs and their association with cognitive impairment

Association of laboratory test results with impaired cognition

As can be seen in figure 3, increased creatinine levels were associated with a higher chance of impaired cognition (OR 1.52, 95%CI 1.17-1.98), as were increased levels of urea (OR 2.14, 95%CI 1.62-2.84). Lower levels of haemoglobin were also associated with a higher chance of impaired cognition (OR 1.92, 95%CI 1.46-2.52, supplemental table S2).

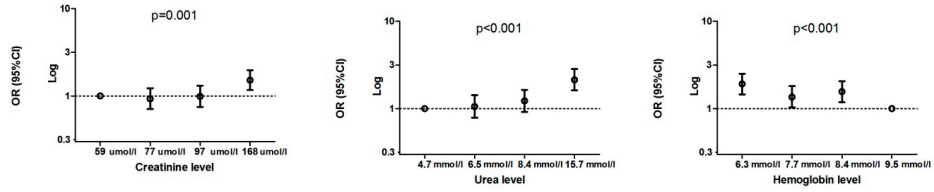

Figure 3: Quartiles of laboratory test results and their association with cognitive impairment

Sensitivity analysis

Results were similar after exclusion of patients with pre-existing dementia, missing 6-CIT score and those with minor trauma. The results of the second sensitivity analysis can be found in supplemental table S3 and show that mean systolic blood pressure, mean arterial pressure, respiratory rate and oxygen saturation, differ between strata of cognitive function. Patients with more severe cognitive impairment had lower systolic blood pressure, lower respiratory rate and lower oxygen saturation.

DISCUSSION

In older patients who present to the ED, cognitive impairment was associated with abnormalities associated with decreased brain perfusion and oxygenation, such as low systolic and diastolic blood pressure, high respiratory rate and low oxygen saturation. There is also an association between laboratory test result that associate with decreased brain perfusion and oxygen delivery such as high urea, high creatinine and low haemoglobin and impaired cognition in this patient group.

Although the association between vital signs and impaired cognition has been studied in the long-term setting[18], our study suggests that in the ED setting this association also exists.

In chronic settings blood pressure variability, blood pressure and cardiac output associate with cognitive impairment in various patient populations[26-28]. Several studies found an association between hypoxia and cognitive impairment in the long-term setting[29, 30].

In addition to vital signs reflecting acute respiratory and organ dysfunction, laboratory tests which are associated with tissue hypoperfusion and oxygen delivery, like creati-

nine, urea and haemoglobin are also associated with cognitive impairment in long-term settings. Siew *et al.* found that in ICU patients elevated levels of creatinine were associated with delirium and coma[31]. Also in patients with chronic end stage renal disease an association with cognitive impairment was found[32]. Overall, the association we find between vital signs and cognitive impairment in the acute setting seems similar to those found in chronic conditions.

Impaired cognition is a frequent finding in the ED setting, with an average incidence of ~30% in the literature[3-7]. Although this may partially be caused by delirium and pre-existing dementia, a part of the incidence of impaired cognition in the ED is unexplained. We hypothesize that in a proportion of patients with impaired cognition this may be related to compromised perfusion or oxygenation of the brain. This could be explained by several pathophysiological mechanisms: first, respiratory rate affects chemoregulation of the brain by changing arterial pCO2 and pH[20]. Second, cardiac output, arterial oxygen saturation and haemoglobin concentration determine oxygen delivery to the brain, potentially affecting cognitive function[33]. Finally, brain perfusion of older patients largely depends on adequate systolic and mean arterial pressures, due to adaptive cerebral vascular changes in old age leading to a shift of the lower limit of autoregulation towards high pressure, with an impaired tolerance to pressure decrease, explaining the association with cognitive function in the acute setting. Impaired brain perfusion and oxygen delivery may even result in local lactate accumulation in the brain, with a possible influence on cognitive function[19].

It should be stressed however that the observational character of the present study should leave room for other possible explanations of this association. First, it is possible that patients with pre-existing cognitive impairment present more ill to the ED because they alarm caregivers in later stages of disease.

Second, patients who are in distress, for example who suffer from dyspnoea, which might be reflected by a high respiratory rate and low oxygen saturation, can focus less on the cognitive test and thereby have a worse score. Third, in the pathophysiological pathway of delirium there seems to be a role for inflammatory cytokines, cholinergic function and the so-called 'aberrant stress response'[34], which might also mediate this association as severe illness such as sepsis, reflected by abnormal vital signs, can start this response of the body[33]. Finally, because both vital signs and delirium are associated with disease severity and mortality, they may reflect two sides of the same coin, rather than a causal relation.

Further studies are therefore necessary in which both brain perfusion/oxygenation and cognition are measured in the acute setting. In these studies a clear distinction between the different pathophysiological mechanisms, such as pre-existing cognitive impairment (i.e. dementia), intercurrent delirium, neurological disorders and brain hypoperfusion or combinations of these, should be made. A next step would then be to investigate the

reversibility of impaired cognition by optimal resuscitation. Finally, it should be assessed whether clinically relevant endpoints such as functional decline and mortality improve if cognitive function is optimized in the acute setting.

This study has several limitations. First, cognition was tested within one hour after arrival to the ED. This could have influenced the cognition score. A patient who is anxious or in pain may perform worse resulting in an overestimation of the incidence of impaired cognition. However, impaired cognition in older patients should always be a trigger for physicians to think further. Second, we did not perform any follow-up measurements of cognitive function and have no information about resuscitative efforts by the Emergency Medical Services or during the ED stay and the influence of this on vital signs. Third, we did not assess presence of delirium using gold standard assessment. Finally, we do not have any measurements of cerebral blood flow. This would be a next step in studying this topic. Strengths of this study are the broad and unselected inclusion in several hospitals and the large sample size. This makes the conclusions more generalisable. Also the low number of missing data makes it possible to draw stronger conclusions. Finally, this is the first large multicentre study to investigate the relationship between vital sign abnormalities and cognitive impairment in the acute setting.

To conclude, we found an association between abnormal vital signs and cognitive impairment in older ED patients. Although this may partially reflect the association of disease severity with delirium, impaired cognition may also be caused by acute disturbance of brain perfusion and oxygenation. This is a first step towards further in-depth studies to investigate whether intervening and improving these vital signs will also improve brain perfusion and cognition. Furthermore it emphasizes the importance for physicians to measure cognition in the ED.

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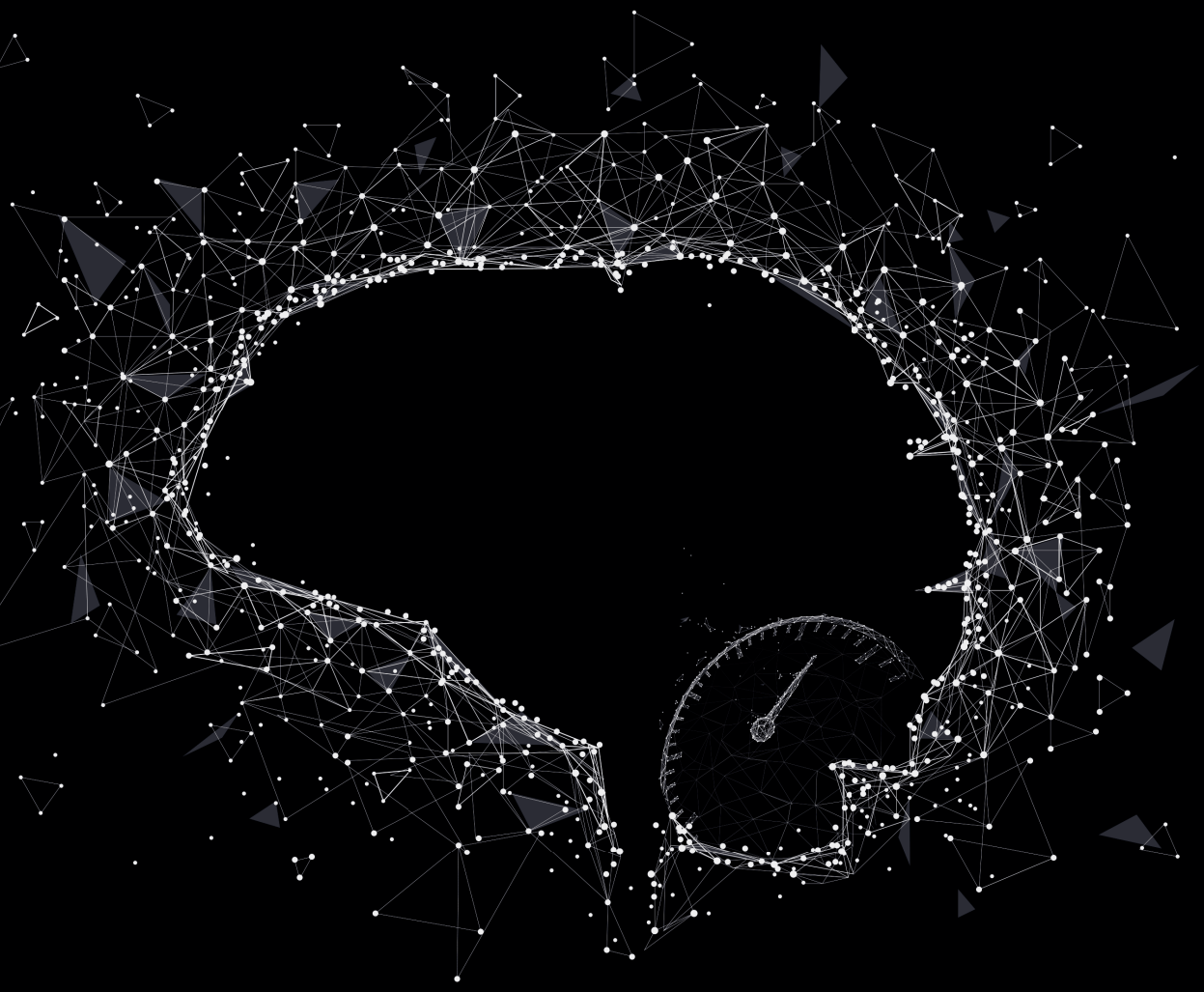

Chapter 9

General discussion

GENERAL DISCUSSION

Key findings

This thesis has four key findings. First, cognitive impairment is associated with adverse outcomes in older ED patients as well as acutely hospitalised older patients. The 6-CIT seems to be a reliable tool to use in ED settings with good correlation with adverse outcomes, in contrast to the CAM-ICU. Second, it is possible to predict adverse outcomes such as hospital admission and mortality in older ED patients using routinely collected clinical data. Third, when adding cognitive impairment and several parameters that can be assessed by the triage nurse to routinely collected parameters, functional decline and mortality of older ED patients can be successfully predicted. Finally, vital signs representing decreased brain perfusion and oxygenation are associated with cognitive impairment.

Identification of cognitive impairment

Cognitive impairment is an under diagnosed disorder in the ED and in this thesis we show it is associated with adverse outcomes in older people. We found that almost one third of older patients in Dutch EDs suffer from cognitive impairment, which means that these patients might be unable to provide accurate information about their medical history and medicine use and puts the patients at risk of not understanding or remembering treatment plans and discharge instructions completely[1]. Delirium and dementia are the most common causes of cognitive impairment in older ED patients. Higher age and dementia are the most important risk factors for developing delirium which adds to the difficulty of making the correct diagnosis of delirium in the ED. Patients with cognitive impairment in the ED have more risk of experiencing adverse events, such as mortality, falls and further cognitive decline, especially in those with pre-existing cognitive impairment. This shows the importance of testing for impaired cognition at an early stage during the ED visit of all older patients[2] to make sure that caregivers recognize cognitive impairment. For this reason, it is for the utmost importance to implement a 'mental status assessment' as vital sign into daily practice at the ED[3].

Reversibility of cognitive impairment by optimal treatment of brain hypoperfusion

A next step would be to assess in the acute setting whether there is a group of patients in which the cognitive impairment is caused by decreased brain oxygenation and perfusion which might be reversible. This follows the general principle of Emergency Medicine in which acute problems are treated first. While the pathophysiology of delirium is still under investigation, there are two proposed pathways. The first is through direct brain insults, such as hypoxia, metabolic abnormalities, stroke and drug effects which

can cause delirium. A second pathway is that of the 'aberrant stress response' in which pro-inflammatory cytokines, elevated cortisol and the GABA system seem to play a role in the disease process secondary to a somatic illness[3-5]. Cognitive impairment caused by either hypoxia and brain hypoperfusion or through delirium (direct brain insult pathway) might be reversible with optimal resuscitation. In chronic conditions such as heart failure and carotid occlusive disease, patients with impaired cerebral blood flow and cognitive function improved when cardiac output improved or when the carotid occlusion was bypassed[6-8]. Similar mechanisms might be at play in the acute setting. When 'cognitive impairment' would be recognized as a vital sign in older patients as a marker of possible severe illness this might help to identify patients in need of aggressive resuscitation[9]. However, there are also specific patient groups, such as patients with severe dementia, in which aggressive treatment is no longer desirable. Future research could include performing gold standard assessments to measure type of cognitive impairment, such as delirium, dementia or other causes, and measuring brain perfusion, at moment of arrival to the ED. Several instruments have been tested to measure brain perfusion and brain activity, such as a transcranial Doppler[10] and EEG measurements[11]. Then, if patients receive adequate resuscitation, follow up measurements of brain perfusion and cognition should clarify whether cognitive impairment due to hypoperfusion of the brain is reversible in the acute setting, as it has been proven in the chronic setting[6]. Finally, it should also be investigated whether improving cognition in the ED due to optimal resuscitation also improves clinically relevant outcomes in short and long term for these patients.

Distinction between various causes of cognitive impairment in the ED setting

Whether it is important to distinguish delirium from dementia in the acute setting is subject to discussion[12, 13]. As mentioned earlier, delirium and dementia are the most common causes of cognitive impairment, both associated with adverse outcome and it is known that the two are strongly linked[4, 12]. A recent study showed little variation in adverse outcomes of patients with different types of cognitive impairment[13]. In our studies we also did not find great variability in the outcomes of older patients with different types of cognitive impairment when performing sensitivity analysis. Furthermore, tools having the ability to distinguish between delirium and dementia by non-specialist care providers, with high acuity, are not readily available[14], and this distinction can be very difficult to make, even for experienced clinicians[4]. It could be argued that a simple test to measure cognitive impairment by all staff working in the ED is more feasible to implement. Finally, in the acute setting making this differentiation has little consequence because the difference between the non-pharmacological treatment of delirium and prevention of delirium in high-risk cases (i.e. dementia) is not always clear, has not

been investigated and comes down to similar principles. The only difference is that in case of delirium the underlying cause should be found. However, in the ED, somatic illness which can be the precipitating factor for delirium such as a possible infection or hypoxemia are looked for in all patients using the ABCDE approach. This makes it unlikely that possible somatic illness causing delirium is overlooked. Therefore, we propose to start non-pharmacological measures in all patients with cognitive impairment in the ED, as they either have delirium or are at high risk of developing delirium. Non-pharmacologic measures to prevent and treat delirium have been proven to be cost-effective in hospitalised older patients[15]. Once patients are out of the acute setting, the cause of the cognitive impairment can be investigated by an experienced specialist trained in mental status assessment, cognitive testing and obtaining information from informants. Pharmacological interventions such as treatment with antipsychotic drugs, such as haloperidol should be reserved only for patients in whom delirium is diagnosed, and only if there is a clinical indication such as failure of non-pharmacological treatment or because of the risk of inflicting damage upon oneself as a result of agitation.
With previous healthcare initiatives it was shown that with a widespread campaign with clear treatment goals it is possible to change the recognition of a disease and its treatment[16, 17]. We propose that a similar program or intervention might also be necessary for the recognition and treatment of cognitive impairment in older patients in the ED.

Screening instruments – different care systems, different solutions?

Several screening instruments for adverse outcomes after a visit to the ED have been described in literature in the last decades, however, these lack accuracy when validated in other study populations[18]. It has been shown that prediction models can behave differently in different patient populations and that implementation of intervention programs is not always successful or reproducible in other settings[19]. One of the reasons for the lack of a global wide implemented screening instrument for older ED patients are differences between care systems, or sometimes even differences within countries; for example, not all Dutch EDs are staffed with ED-physicians. Furthermore, nomenclature such as 'frailty', 'crowding', 'acute wards' and 'Emergency Departments' could be defined entirely different[20, 23], and mean length of stay can vary greatly between countries[21, 22]. EDs can be staffed with different teams of varying expertise, which can have influence on patient satisfaction and patient flow[23]. Some tools that might not work in the Netherlands, for example the CAM-ICU as we showed **chapter 7**, might work in systems were patients stay in the ED for longer amounts of time. In **chapter 6** we describe the successful derivation and external validation of the APOP-screener in the Netherlands. The APOP-screener can be used to predict functional decline and mortality, as well as screen for cognitive impairment, in older patients at the moment of arrival to the ED.

Above mentioned arguments however could also mean the APOP-screener and intervention package cannot be copied one on one to other countries.
Several taskforces for European and worldwide collaboration on GEM have been established in the last years. The focus of these groups should be to find similarities in problems of older patients in the ED between care systems. They should facilitate the development of universal toolboxes which contain screeners for risk stratification, cognitive impairment, and proposed interventions that can be amended to the local situation, from which individual care systems and patients can profit. These toolboxes should be adequately distributed, after which it should be assessed whether this also improves clinically relevant outcomes for older patients and is cost-effective. This could be done by performing impact studies using tools such as the RE-AIM framework to assess which screeners and interventions work for different care systems.

Future perspectives

In the APOP-study we have performed several pilots with nurses working in the ED to see if the APOP-screener was feasible, as described in **chapter 6**. After feedback of the nurses changes were made to the lay-out and items in the screener. Currently we are implementing the APOP-screener in one hospital to screen for cognitive impairment and risk of adverse outcomes on a wide scale and will evaluate its feasibility and impact using the RE-AIM framework[24]. If it is possible to use the APOP-screener in clinical practice for a longer period of time, the final step would be to assess whether it also improves outcomes for older patients in larger multicentre studies. If successful, wide dissemination and implementation of the APOP-screener in the Netherlands would be next.
This thesis describes one of the first multidisciplinary initiatives in the Netherlands in which Internal Medicine, Geriatric Medicine and Emergency Medicine work together in the field of Geriatric Emergency Medicine (GEM). To improve and propagate GEM throughout training programs of several medical specialties and EDs in the Netherlands is one of the future goals.

Clinical implications

This thesis brings forward several important findings for clinical practice. First of all, we propose a workflow which provides optimal care for older patients with cognitive impairment as can be seen in figure 1. In this workflow we show how the APOP-screener (**chapter 6**) can be used in clinical practice to detect patients with cognitive impairment and how caregivers in the ED can act accordingly. Secondly, this thesis provides a basis for further development and implementation of frailty screeners for older ED patients. The APOP-screener can also be used to assess which patients have cognitive impairment and who have the highest risk of adverse outcomes and could make it possible to ad-

equately distribute resources in a system which is already working at its threshold, as has been deemed a priority in recent literature[25]. Alternative interventions and workflows can be invented and implemented to prevent delirium and adverse outcomes in older ED patients at risk using the APOP-screener. Furthermore, as described in **chapter 7**, we warrant caution to use the CAM-ICU as screener for delirium in care systems were older people have a relatively short ED length of stay.

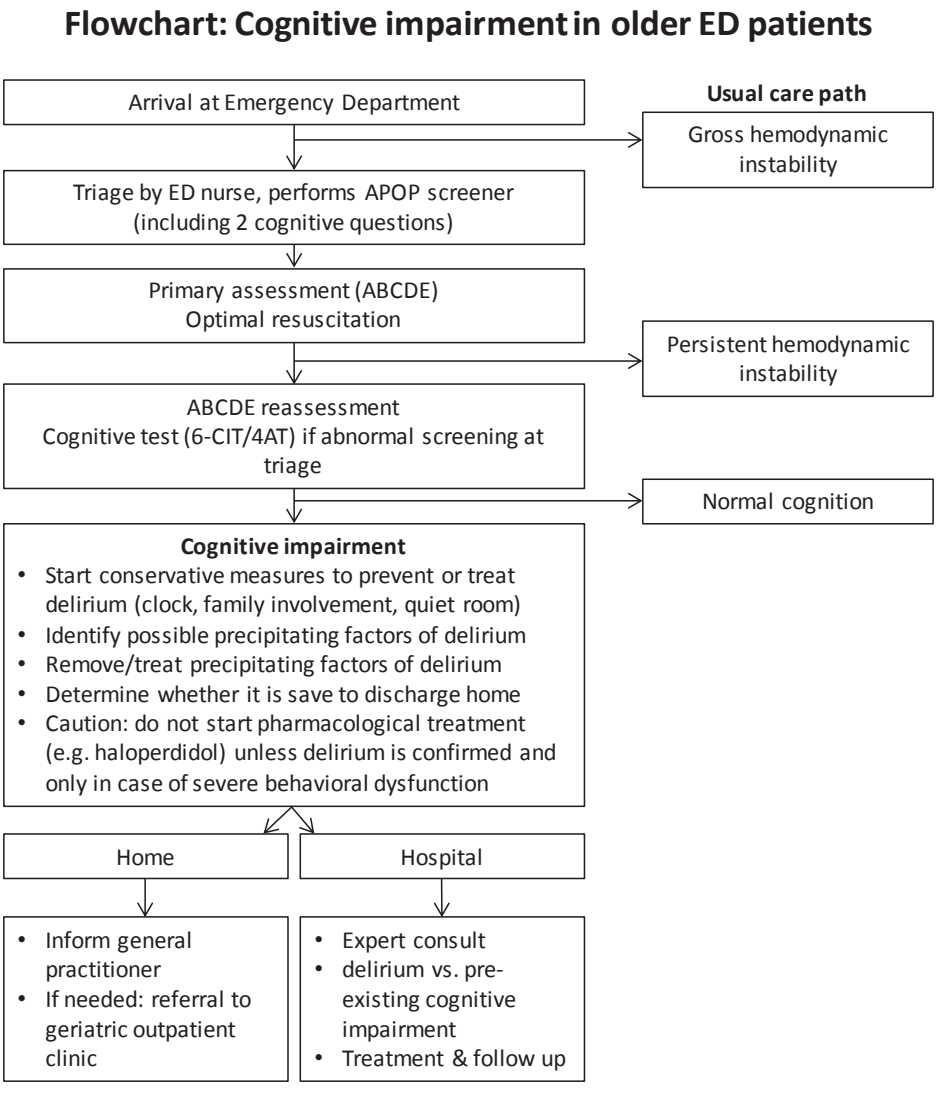

Figure 1. Flowchart: Cognitive impairment in older ED patients

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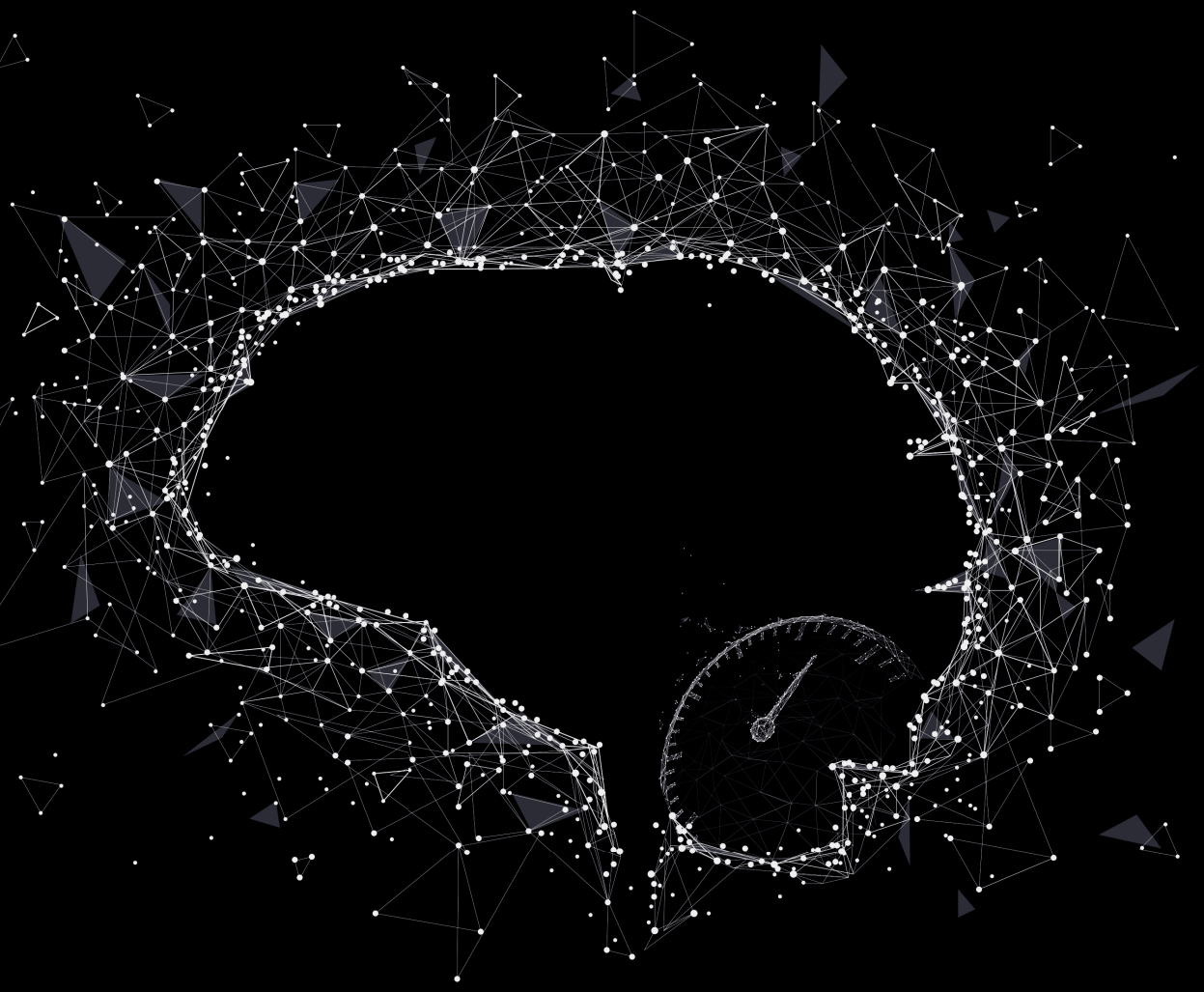

Chapter 10

English summary

Nederlandse samenvatting

List of co-authors

List of publications

Curriculum vitae

Dankwoord

ENGLISH SUMMARY

Introduction

The number of older people in the population is rising and so is the number of older patients in the Emergency Department (ED)[1]. Older patients often have complex problems which leads to an increased chance of repeat ED visits, longer length of stay, higher chance of hospital admission and higher chance of negative health outcomes after a visit to the ED[2]. Cognitive impairment is a frequent problem in older ED patients, with an estimated prevalence of 20-40%[3-5]. Unfortunately cognitive impairment often remains unrecognized[3] and little is known about the association between cognitive impairment and adverse outcomes in older ED patients.

Aim of this thesis

The aim of this thesis is threefold. The primary aim of this thesis is to investigate whether cognitive impairment is associated with adverse outcomes in acutely presenting older patients. The second aim is to assess whether routinely collected parameters in addition to cognitive impairment can be used to screen for high risk of adverse outcome in older ED patients. The third aim is to investigate whether a proportion of older ED patients might have cognitive impairment due to impaired brain perfusion and oxygenation.

Summary of key findings

This thesis is divided in two parts. The first part discusses the association between cognitive impairment and adverse outcomes in acutely presenting older patients. In **chapter 2** we investigated older patients who were acutely hospitalised. During four month periods in three consecutive years we included patients aged 70-years or older and performed the Six-Item Cognitive Impairment Test (6-CIT) to measure cognitive function. One in six older patients suffered from cognitive impairment and these patients had a higher chance of 90-day functional decline and mortality. When corrected for age, sex, living situation and treating medical specialist this association was no longer statistically significant. Cognitive impairment was independently associated with prolonged hospital length of stay, admission to a nursing home and in-hospital mortality.

In **chapter 3** we investigated older patients in the Emergency Department of three different hospitals. We found that nearly 30% of older ED patients suffered from cognitive impairment. Three and twelve months after the ED visit we determined whether patients had endured functional decline or mortality. There is an association between cognitive impairment and adverse outcomes, irrespective of the cause of the cognitive impairment. This association was independent of age, disease severity and comorbidi-

ties. In a sub-analysis we found that this association was similar for patients who were hospitalised and those who were sent home.

The second part of this thesis consists of multiple chapters which describe prediction models and screening instruments used to identify older ED patients with a high risk of adverse events.

In **chapter 4** we used a retrospective cohort of all patients aged 70-years and older who visited the ED of the Leiden University Medical Center during a 1-year period. We created a prediction model using routinely collected parameters, such as age, vital signs and the indication to perform laboratory testing. These routinely collected parameters can be used at arrival of older patients to the ED to predict 90-day mortality. The strongest predictors were indication to perform laboratory testing, hypothermia, referral from another hospital and low oxygen saturation levels. These data were used to determine the parameters which we investigated in the prospective APOP-study.

In **chapter 5** we also used a retrospective cohort study of all ED visits of the Leiden University Medical Center during a one year period. For this study both younger and older patients were included. We showed that hospital admission can be predicted at arrival to the ED using routinely collected parameters. Different prediction models were made for younger and older patients. The strongest predictors for hospital admission were age, sex, triage category, arrival via ambulance, indication to perform laboratory testing, main complaint, responsible medical specialist and all measured vital signs. The model for younger patients had better overall predictive capabilities with a higher area under the curve. The model for older patients was better suited to identify those patients with the highest risk, with a higher positive predictive value.

In **chapter 6** we describe the main results of the APOP-study. We performed a prospective cohort study in four hospitals in which we collected data of older people at arrival to the ED. After three and twelve months we determined whether they suffered adverse events (functional decline or mortality). In this chapter we show how the previously created APOP-screener[6] was updated. Amongst other things, cognitive impairment was added as predictor. The other parameters in the model are age, sex, arrival by ambulance, needing help on a regular basis, needing help with bathing and hospitalisation in the past six months. The calibration and discrimination of the model were good and a group of patients with a high positive predictive value could be successfully identified.

In **chapter 7** we used the prospective data of the APOP-study of two hospitals. We performed the CAM-ICU, a delirium screener, within one hour of arrival of older patients to the ED. Using this screener we found an unexpectedly low delirium incidence of 1%. This was compared to another method of diagnosing delirium, the 6-CIT with a cut-off point of ≥14 points, where we found a delirium incidence of 10%. This last prevalence is comparable to previously published literature. The CAM-ICU might not be suitable for early detection of delirium in the ED.

In **chapter 8** we used the prospective data of the APOP-study of four hospitals. At arrival to the ED cognitive function was assessed using the 6-CIT, after which we looked at the association between vital signs, as a measure of acute hemodynamic changes, and cognitive impairment. Vital signs that associate with decreased brain perfusion and oxygenation, such as a low systolic and diastolic blood pressure, as well as a low mean arterial pressure, high respiratory rate and low oxygen saturation were associated with cognitive impairment. An association between high levels of creatinine, high levels of urea, low levels of haemoglobin and cognitive impairment was also found. This might partially reflect the association of disease severity with delirium, but may also be caused by acute disturbance of brain perfusion. If a part of cognitive impairment in older ED patients is caused by acute disturbance of brain perfusion and oxygenation, this might mean it could be reversed by optimal resuscitation.

Discussion

As mentioned previously, cognitive impairment is frequently missed in the ED[3]. To prevent cognitive impairment to be underdiagnosed it is important to implement a standard evaluation of cognitive function, in all older patients and using a validated instrument, into daily practice[7]. Although we would like to emphasize that recognizing cognitive impairment in all older ED patients should have the priority, a next step would be to identify patients in whom cognitive impairment might be reversible. In patients with chronic hypoperfusion of the brain, for example in the case of chronic heart failure, it was proven that cognitive function improved when cardiac function did[8, 9]. It is possible this 'heart-brain association' might also be applicable to older patients in the acute setting. Measuring brain perfusion and oxygenation and the effects of optimal resuscitation on cognitive function is a subject which should be further investigated in the future. When cognitive impairment remains existing despite optimal resuscitation it is of great importance to start conservative measures in the ED to prevent or treat delirium. If patients are hospitalised well-trained specialists can make the diagnosis of delirium vs. dementia. An example of a workflow for optimal treatment of older patients with cognitive impairment in the ED can be found in the discussion of this thesis.

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NEDERLANDSE SAMENVATTING

Introductie

Het aantal oudere mensen in de bevolking neemt toe en daarmee ook het aantal oudere patiënten op de Spoedeisende Hulp (SEH)[1]. Oudere patiënten hebben met hun vaak complexe problematiek een grote kans op herhaalbezoeken, hebben gemiddeld een langere ligduur op de SEH, een grotere kans op opname in het ziekenhuis en een vergrote kans op negatieve gezondheidsuitkomsten na een bezoek aan de Spoedeisende Hulp[2]. Cognitieve beperkingen zijn een veelvoorkomend probleem bij oudere SEH patiënten, met een prevalentie van cognitieve stoornissen die rond de 20-40% geschat wordt[3-5]. Helaas worden deze cognitieve stoornissen vaak niet herkend[3] en is er weinig duidelijk over de relatie tussen cognitieve stoornissen en negatieve gezondheidsuitkomsten bij oudere patiënten op de Spoedeisende Hulp.

Doel van dit proefschrift

Het doel van dit proefschrift is drieledig. Het eerste doel is om te onderzoeken of cognitieve stoornissen geassocieerd zijn met negatieve uitkomsten bij acuut presenterende oudere patiënten. Het tweede doel is om te onderzoeken of routinematig verzamelde parameters en cognitieve stoornissen gebruikt kunnen worden om oudere SEH patiënten te screenen en een groep te identificeren met een hoog risico op negatieve gezondheidsuitkomsten. Het derde doel is om te onderzoeken of er een groep oudere patiënten is, waarvan de cognitieve stoornissen worden veroorzaakt door verminderde breinperfusie en oxygenatie.

Overzicht van het beschreven onderzoek

Dit proefschrift is onderverdeeld in twee delen. In het eerste deel wordt de associatie tussen cognitieve stoornissen en het optreden van negatieve gezondheidsuitkomsten bij acuut presenterende oudere patiënten beschreven. In **hoofdstuk 2** onderzochten we oudere patiënten die acuut opgenomen waren in het ziekenhuis. Gedurende periodes van vier maanden in drie opeenvolgende jaren werden in meerdere ziekenhuizen alle patiënten van 70 jaar en ouder geïncludeerd, waarbij de Six-Item Cognitive Impairment Test (6-CIT) werd afgenomen om cognitieve stoornissen vast te stellen. Een op de zes oudere patiënten had cognitieve stoornissen en deze patiënten hadden een hogere kans op negatieve gezondheidsuitkomsten na 90 dagen. Wanneer hierbij gecorrigeerd werd voor leeftijd, geslacht, woonsituatie en behandelend medisch specialist was deze associatie niet meer statistisch significant. Wel was er een onafhankelijke relatie tussen cognitieve stoornissen en verlengde ligduur in het ziekenhuis, verhoogde kans op sterfte tijdens ziekenhuisopname en een hogere kans op opname in het verpleeghuis na ontslag.

In **hoofstuk 3** onderzochten we oudere patiënten op de Spoedeisende Hulp van drie verschillende ziekenhuizen. We toonden aan dat bijna 30% van de oudere patiënten op de Spoedeisende Hulp cognitieve stoornissen heeft. Na 3 en 12 maanden na het SEH bezoek werd vastgesteld of er sprake was van functionele achteruitgang of overlijden. Hierbij bleek er een relatie te bestaan tussen cognitieve stoornissen en negatieve gezondheidsuitkomsten, ongeacht de onderliggende oorzaak van de cognitieve stoornissen. Deze relatie was onafhankelijk van leeftijd, ziekte ernst en co-morbiditeit. In een sub-analyse bleek tevens dat patiënten die vanaf de SEH naar huis werden ontslagen of opgenomen in het ziekenhuis, vergelijkbare negatieve gezondheidsuitkomsten hadden.

In het tweede deel beschrijven we verschillende predictiemodellen en screeningsinstrumenten die oudere patiënten op de Spoedeisende Hulp met een hoog risico op negatieve gezondheidsuitkomsten moeten identificeren. In **hoofdstuk 4** werd een retrospectief cohort verzameld van alle patiënten van 70 jaar en ouder die gedurende een jaar de Spoedeisende Hulp van het LUMC bezochten. We maakten een predictiemodel met routinematig verzamelde gegevens, zoals leeftijd, vitale parameters en de noodzaak tot het verrichten van bloedonderzoek. Deze routinematig verzamelde parameters kunnen voorspellen welke patiënten een hoge kans hebben op sterfte in de 90 dagen na een bezoek aan de Spoedeisende Hulp. De sterkste voorspellers waren het verrichten van bloedonderzoek, hypothermie, verwijzing vanuit een ander ziekenhuis en een lage zuurstofsaturatie. Deze gegevens zijn gebruikt om de parameters te bepalen die in de prospectieve APOP-studie werden verzameld.
In **hoofdstuk 5** werd tevens gebruik gemaakt van een retrospectief cohort dat alle SEH bezoeken van het LUMC van een jaar behelst. Voor deze studie werden zowel jonge als oude patiënten geïncludeerd. We toonden aan dat ziekenhuisopname voorspeld kan worden door middel van routinematig verzamelde gegevens die bij aankomst op de Spoedeisende Hulp al bekend zijn. Er werden aparte predictiemodellen gemaakt voor jongere en oudere patiënten. De sterkste voorspellers voor ziekenhuisopname waren leeftijd, geslacht, triagecategorie, aankomst middels ambulance, noodzaak tot bloedonderzoek, hoofdklacht, behandelend medisch specialisme en alle gemeten vitale parameters. Het model voor jongere patiënten voorspelde over het algemeen beter, maar het model voor oudere patiënten was beter geschikt om een groep patiënten met het hoogste risico te identificeren.
In **hoofdstuk 6** worden de hoofdresultaten van de APOP-studie beschreven. Er werd een prospectief onderzoek verricht in vier ziekenhuizen waarbij gegevens werden verzameld van oudere patiënten bij aankomst op de SEH. Na drie en twaalf maanden werd vastgesteld of er sprake was van functionele achteruitgang of overlijden. In dit hoofdstuk laten we zien hoe de eerder ontwikkelde APOP-screener[6] een update heeft ondergaan. Onder andere cognitieve stoornissen zijn als predictor toegevoegd in het

model. De overige parameters in het model zijn leeftijd, geslacht, aankomst per ambulance, regelmatig hulp nodig hebben, ondersteuning nodig hebben bij douchen en opname in het ziekenhuis in de afgelopen zes maanden. De kalibratie en discriminatie van het model zijn goed en een groep patiënten met het hoogste risico op negatieve gezondheidsuitkomsten kon succesvol worden geïdentificeerd.

In **hoofdstuk 7** is gebruik gemaakt van de prospectief verzamelde data van twee ziekenhuizen. Bij oudere patiënten is binnen een uur na aankomst op de SEH de CAM-ICU, een screener voor het vaststellen van delier, afgenomen. Hierbij werd een onrealistisch lage prevalentie van delier gevonden van 1%. Wanneer we een andere methode gebruikten om delier vast te stellen, de 6-CIT score met een afkappunt van ≥14, vonden we een prevalentie van ongeveer 10% wat overeenkomt met hetgeen in de literatuur beschreven wordt. De CAM-ICU is dus mogelijk niet geschikt is voor vroegtijdige herkenning van delier op de Spoedeisende Hulp.

In **hoofdstuk 8** zijn de prospectieve gegevens van de vier ziekenhuizen die deelnamen aan de APOP-studie gebruikt. Bij aankomst op de Spoedeisende Hulp werd cognitie gemeten middels de 6-CIT, waarna we hebben gekeken naar de associatie tussen vitale parameters, als weergave van acute hemodynamische veranderingen, en cognitieve beperkingen. Vitale parameters die samengaan met verminderde breinperfusie en oxygenatie, zoals een lage bloeddruk, hoge ademhalingsfrequentie en lage zuurstofsaturatie, zijn geassocieerd met cognitieve beperkingen in oudere patiënten op de Spoedeisende Hulp. Dit zou deels kunnen worden verklaard door de associatie tussen deze afwijkende vitale parameters, ziekte-ernst en delier. Het is echter ook goed mogelijk dat een deel van de cognitieve stoornissen die oudere patiënten op de Spoedeisende Hulp ervaren wordt veroorzaakt door verminderde oxygenatie en perfusie van het brein. Als dit het geval is, is het mogelijk dat een deel van deze cognitieve stoornissen reversibel is.

Discussie

Zoals eerder beschreven worden cognitieve stoornissen op de Spoedeisende Hulp vaak over het hoofd gezien[3]. Om te voorkomen dat cognitieve stoornissen gemist worden, is het belangrijk dat een standaard evaluatie van het cognitieve vermogen bij alle oudere patiënten en door middel van een gevalideerd instrument, wordt ingevoerd in de dagelijkse praktijk[7]. Hoewel we willen benadrukken dat het herkennen van cognitieve stoornissen, ongeacht de oorzaak, bij alle oudere patiënten op de Spoedeisende Hulp prioriteit moet krijgen, is een volgende stap om de patiënten bij wie de cognitieve stoornissen reversibel te zijn te identificeren. Bij chronische perfusieproblemen van het brein, zoals bijvoorbeeld bij chronisch hartfalen, is bewezen dat wanneer de breinperfusie verbetert hetzelfde gebeurt met het cognitief functioneren[8, 9]. Mogelijk zou deze 'hart-brein associatie' ook voor een deel van de oudere patiënten in de acute setting het geval kunnen zijn. Het meten van breinperfusie en oxygenatie en de effecten van

optimale resuscitatie op cognitieve stoornissen is een onderwerp dat in de toekomst verder moet worden onderzocht.
Wanneer de cognitieve stoornissen ondanks optimale resuscitatie blijven bestaan, is het van belang om tijdens het verblijf op de Spoedeisende Hulp te starten met conservatieve maatregelen voor het behandelen of voorkomen van een delier. Bij opname in het ziekenhuis kan dan door goed geschoolde medewerkers de differentiatie tussen delier en dementie worden gemaakt. Een voorbeeld van een stroomschema voor optimale behandeling van ouderen met cognitieve stoornissen op de SEH is weergegeven in de discussie van dit proefschrift.

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CURRICULUM VITAE

Jacinta Lucke werd op 28 februari 1988 geboren te Amsterdam. Zij behaalde haar VWO-diploma in 2006 aan het Eerste Christelijk Lyceum te Haarlem. Daarna volgde zij de studie Geneeskunde aan de Universiteit Leiden, die zij voltooide in 2013. Tijdens haar studie raakte zij geïnteresseerd in spoedzorg voor ouderen. Na het afronden van haar studie werkte zij als arts-assistent op de Spoedeisende Hulp in het LUMC. Dit combineerde ze met het doen van onderzoek binnen het vakgebied Ouderengeneeskunde, bij de APOP-studie.

In 2014 begon zij met haar opleiding tot SEH-arts in het LUMC bij dr. C. Heringhaus. Tegelijkertijd deed zij promotieonderzoek binnen de Ouderengeneeskunde onder begeleiding van prof. dr. G.J. Blauw. Zij presenteerde haar werk op meerdere nationale en internationale congressen en werd benoemd tot vice-voorzitter van de sectie 'Geriatric Emergency Medicine' van de Europese vereniging voor Spoedeisende Hulp artsen (EUSEM). Sinds december 2018 werkt zij als SEH-arts in het Spaarne Gasthuis.

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