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Cognitive impairment in older emergency department patients

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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 $\mu\text{mol/liter}$, 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 (available 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.

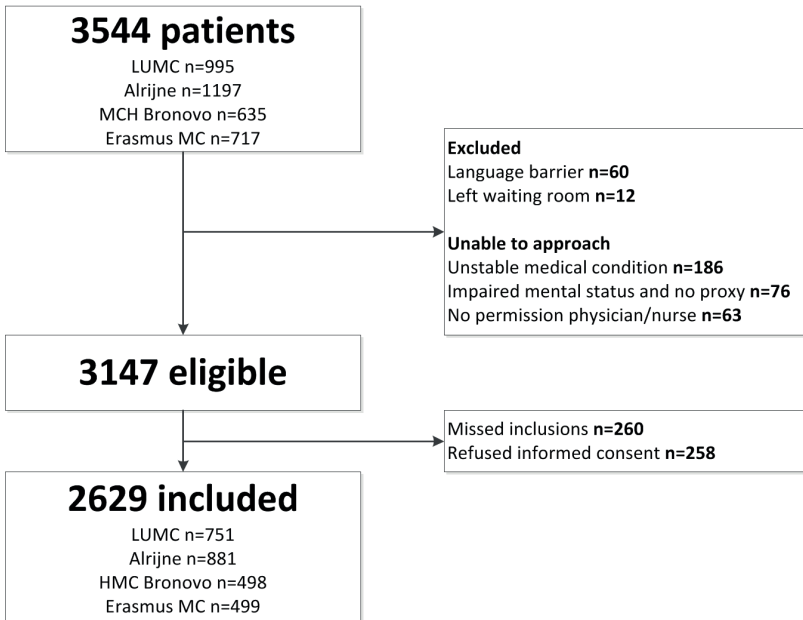


Figure 1: Flowchart of study population

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
<u>ED presentation characteristics</u>	
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)
<u>Vital signs</u>	
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, °C	36.9 (0.9)
Capillary refill, sec, median (IQR)	2 (2-3)
<u>Geriatric characteristics</u>	
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, °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).

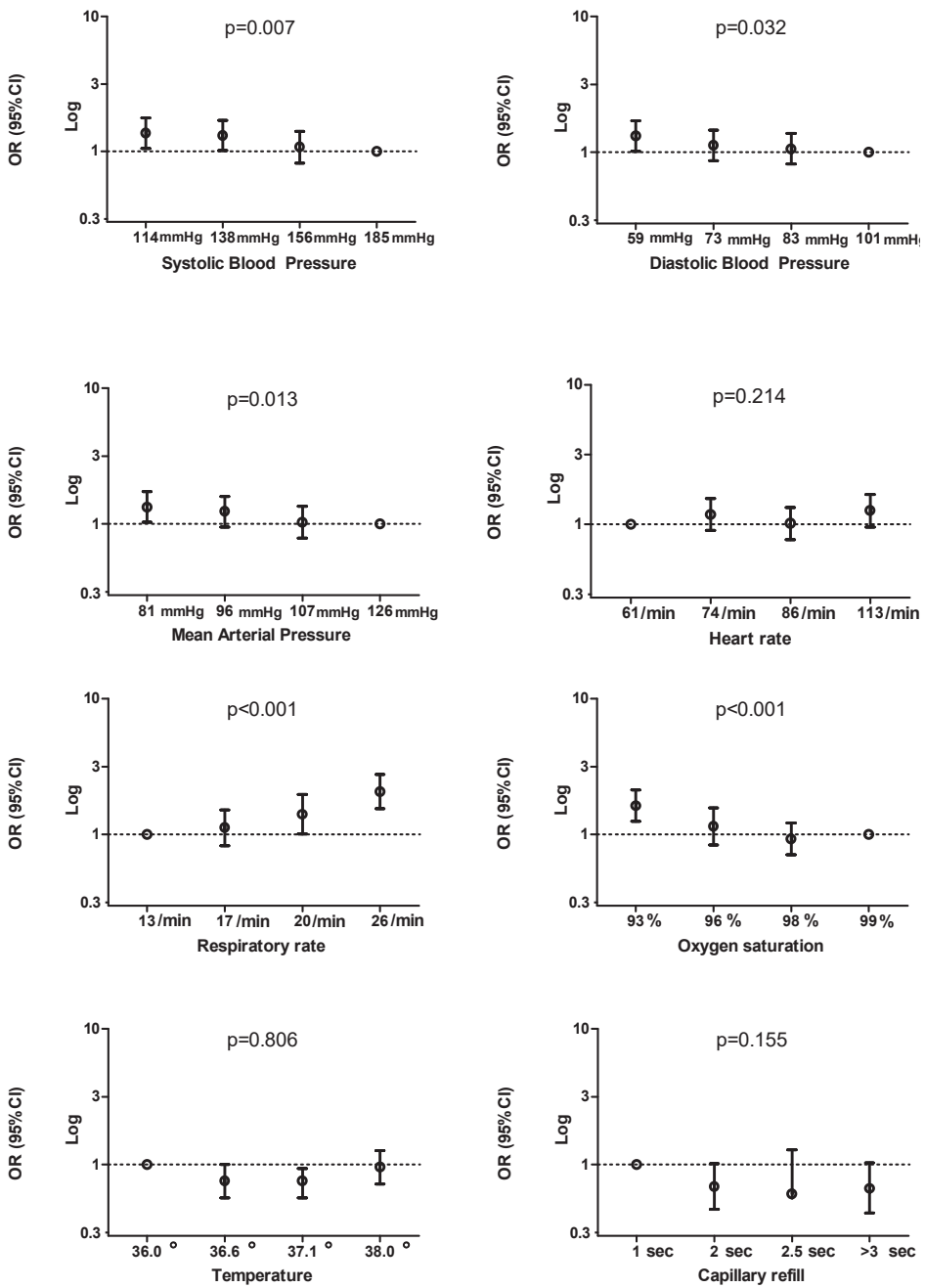


Figure 2: Quartiles of vital signs and their association with cognitive impairment

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).

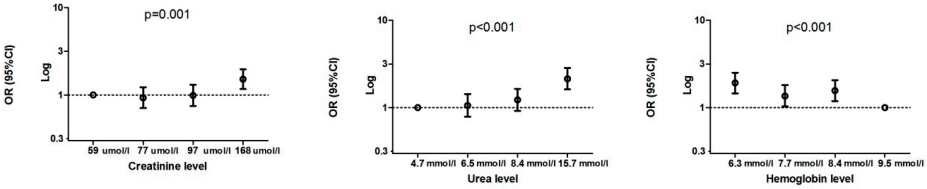


Figure 3: Quartiles of laboratory test results and their association with cognitive impairment

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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