BMJ Open Root causes and preventability of emergency department presentations of older patients: a prospective observational study

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ABSTRACT

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Dr Babiche Driesen: b.driesen@amsterdamumc.nl **Objective** More older patients are presenting to the emergency department (ED). It is important to know why these patients present and if the ED is the best place for them to receive the care they need. The primary aim of this study was to identify organisational-related, technicalrelated, healthcare worker-related and patient-related factors leading to ED presentations of older patients. The secondary aim was to determine patients' and caregivers' perspectives on what kinds of ED presentations are potentially preventable.

Design This is a prospective observational study. A root cause analysis was performed by the Prevention and Recovery Information System for Monitoring and Analysis method. It used basic administrative data collected from patient records and interviews of patients, general practitioners (GPs) and physicians at the ED. Setting The ED of an academic hospital in the

Netherlands.

Participants 100 older patients (aged ≥70 years) who attended the ED between November 2017 and March 2018.

Results In 100 patients presenting to the ED, 159 factors that contributed to presentation were identified; most of these factors were related to underlying diseases (59%) and patient-related factors (18%). These presentations were considered potentially preventable by 23% of the physicians at the ED and 21% of the GPs, but only 10% of the patients. In only four cases was there overall agreement between the patients and the healthcare workers.

Conclusion The most frequent underlying factors contributing to an ED presentation in older patients are disease-related and patient-related. The low percentage of ED presentations considered potentially preventable shows that a 'preventable ED presentation' is difficult to define and therefore interventions to reduce them are unlikely to be simple. Novel solutions within the acute care pathway are required in order to deliver care of optimal quality and safety to older patients.

INTRODUCTION

As the world population is ageing rapidly, older patients are an important patient group visiting emergency departments (EDs).

Strengths and limitations of this study

- ► Factors directly contributing to emergency department (ED) presentations of older patients were explored using the Prevention and Recovery Information System for Monitoring and Analysis method and classified using the Eindhoven Classification Model.
- Patients and their general practitioners and phy-sicians at the ED were interviewed concerning the causes and potential preventability of ED presentations.
- A major strength of this study is the inclusion and comparison of patients' and healthcare workers' perspectives.
- A limitation of this study is that it only considered ED presentations during the peak hours due to availability of researchers.

Protected by copyright, including for uses related to text and data mini Currently, they account for up to 38% of all ED presentations, ^{1 2} and the percentage of ≥ people aged 65 years and over in European trair countries is forecast to increase from 14% in 2010 to 25% in 2050.³

ıng, Older patients often present with atypical symptoms and complex health problems with multiple comorbidities.^{1 2 4–7} Patients with non-specific complaints are often undertriaged in the ED despite the high prevalence of $\overline{\mathbf{a}}$ serious underlying conditions.⁸ In addition, older patients may have impaired cognition, communication problems, reduced social support and malnutrition and suffer from & abuse or neglect, all of which may contribute **3** to ED presentations and influence outcomes.⁶ These factors may negatively affect the care received at the ED, leading to more investigations, more specialist consultations and longer lengths of ED stay.¹⁵

Greater understanding is needed of those factors that influence ED utilisation by older patients. Once an older patient has presented to an ED, even if the presentation was potentially preventable, they may be more likely to continue to use ED services and experience high rates of hospitalisation and functional decline, with higher risk of subsequent mortality.⁶⁷ Therefore, although the current literature does not provide a standard definition,⁹⁻¹¹ preventable ED presentations should be avoided and replaced by more valuable and appropriate care alternatives, such as home care, general practitioner (GP) or other community-based services. Furthermore, we believe understanding older patients' and healthcare workers' perspectives is critical to optimisation of emergency care.

The main aim of this study was to identify organisationalrelated, technical-related, healthcare worker-related and patient-related factors that contribute to ED presentations of older patients. The secondary aim was to gather more insight into patients' and caregivers' opinions on the potential preventability of these ED presentations.

MATERIALS AND METHODS Study design

This is a prospective observational study of 100 older patients (≥ 70 years) who presented to the ED of the Amsterdam UMC location VU University Medical Centre (VUMC) in Amsterdam from 20 November 2017 to 8 March 2018.

Study setting and population

The VUMC is an urban academic level 1 trauma centre with 733 beds, approximately 50000 hospital admissions and 30000 ED presentations per year. Internal hospital data for the year 2017 indicate that there were approximately 4650 patients aged 70 years and older visiting the ED, resulting in 5500 ED presentations.

We included patients aged 70 years and older who were able to give informed consent. Patients who were unable to give informed consent or were critically ill were excluded. We also excluded patients living in an assisted living facility or a nursing home because they were considered a different patient population and already receiving continuous institutional care. The population studied was a convenient sample of 100 patients who presented from Monday to Friday during daytime when trained researchers to interview them were available. There is no valid method to perform a sample size calculation or a power analysis for a PRISMA (Prevention and Recovery Information System for Monitoring and Analvsis) profile.^{12 13} However, Smits *et al*¹⁴ state that when the number of analysed events is at least 50, the variety of possible unintended events will be captured and a valid causal factor profile can be drawn.

Patient and public involvement

Patients were not involved in setting the research question, the outcome measures, or the design or implementation of the study. Moreover patients were not asked to advise on the interpretation or documentation of results.

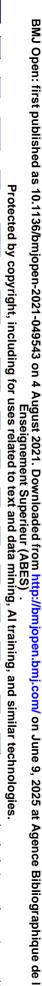
Data collection and measurements

Patients who met the inclusion criteria were approached by a member of the research team to obtain written consent. Semistructured patient interviews were performed by a trained researcher while the patient was in the ED (online supplemental appendix 1). One of the aims of the interview was to gather insight into the causes of the ED presentation, the patient's health status and living situation, and the patient's opinion on factors that contributed to their ED presentation. Additionally, the 'acute presenting older patient (APOP)' scores¹⁵ were calculated based on patient age, gender, arrival by ambulance, need for regular assistance, need for assisthat contributed to their ED presentation. Additionally, tance with bathing/taking a shower, hospitalisation in Z the prior 6 months and impaired cognition. The APOP 8 score is expressed as a percentage and identifies the individual risk of 90-day functional decline or mortality in ED patients aged \geq 70 years. The threshold for a 'high risk' is ≥45%.

The opinion on the potential preventability of the ED presentation was asked using the following question: 'Do you feel this current ED presentation was preventable in any way, by anyone?' Possible options were 'yes', 'no' and uses r 'don't know', followed by an explanation of their answer. The patient's GP and their attending physician at the ED were interviewed within 3 days by either telephone or mail, and asked factors they considered contributed to the ED presentation and if it was potentially preventable. Additional data were gathered through the electronic 5 patient records, which included patient characteristics and ED presentation details, which were then tabulated in a standardised data collection form. Six weeks after inclusion in the study, a follow-up telephone interview with the patient was performed (online supplemental E appendix 1). When contact with the patient was not possible, the researchers contacted their GP based on the ≥ consent already provided by the patient during inclusion.

Data analysis: PRISMA

training The PRISMA method identifies the root causes contributing to an incident or event through the creation of a causal tree (online supplemental appendix 2). However, determining the root cause of an event does not necessarily imply that the event is potentially preventable. The PRISMA method has been accepted for incident analysis by the World Alliance for Patient Safety by the WHO^{12 13} and consists of three main steps: (1) incident description, (2) cause classification and (3) translation to **\overset{\circ}{\mathbf{G}}** structural measures. Two medically and PRISMA-trained researchers (RB, HM) each constructed a causal tree from the information obtained from the interviews and the patient's electronic medical record. The top of each tree consisted of the event, in this case the presentation at the ED, followed by its direct causes, which were identified by asking why the ED presentation had occurred. Subsequently indirect causes were systematically exposed by constantly asking 'why' the event had taken place. An example of a root causal tree is displayed in figure 1.



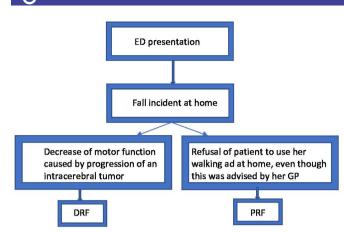


Figure 1 Example of a root causal tree. DRF, diseaserelated factor; ED, emergency department; GP, general practitioner; PRF, patient-related factor.

Root causes were then classified as technical-related, organisational-related, human-related and patient-related factors using the Eindhoven Classification Model (ECM).¹²¹³ The root causal trees of both researchers were compared and discussed with a third PRISMA-trained investigator (BD) until consensus was reached. Following the recommendations of Fluitman *et al*,¹⁶ disease-related root causes were added to the ECM root causes. In the final step, the PRISMA profile was made and prevention recommendations can be directed at the most frequently occurring root causes.

Data analysis: statistical analysis

In SPSS V.22.0 descriptive characteristics and frequencies were calculated to describe patient characteristics, root causes and preventability. Categorical outcome measures are presented as frequencies and percentages. To gather insight into patients' health status and whether the ED is the most appropriate location within the acute care pathway at the time of presentation to the ED, we divided the patients into two groups: a group of patients admitted to the hospital and a group of patients discharged home after the ED presentation. For the subgroup analysis we used the Pearson's χ^2 for dichotomous and categorical data. The independent samples t-test was used for continuous variables. Differences were considered statistically significant at a p value less than 0.05.

RESULTS

Patient characteristics

During the study period 382 patients aged 70 years and older presented while a researcher was present at the ED, but 282 patients were excluded because (1) they were living in an assisted living facility or nursing home (n=149, 52.9%), (2) they were not asked to participate (n=28, 9.9%), (3) they refused to give informed consent (n=59, 20.9%) or (4) they were unable to give informed consent (n=46, 16.3%).

The median age of the final study population of 100 patients was 76 years (IQR 12) and 55% were male

Table 1 Patient characteristics	
n (%)	100 (100%)
Age, median (IQR)	76 (12)
Male	55 (55)
Independent living situation prior to ED presentation	100 (100)
Home care	16 (16)
Living alone	47 (47)
ED presentation 30 days prior to current ED presentation	7 (7)
ED presentation 1 year prior to current ED presentation	22 (22)
ED presentation related to ED presentation in the last year prior to ED presentation	14 (14)
Hospital admission 30 days prior to ED presentation	9 (9)
Hospital admission 1 year prior to ED presentation	33 (33)
ED presentation related to hospital admission in the last year prior to ED presentation	23 (70)
Medical specialty*	
Surgery	3 (3)
Orthopaedic	1 (1)
Emergency medicine	35 (35)
Internal medicine	18 (18)
Pulmonary medicine	11 (11)
Gastroenterology	4 (4)
Nephrology	2 (2)
Rheumatology	2 (2)
Oncology	2 (2)
Neurology	19 (19)
Urology	2 (2)
Jaw surgery	1 (1)
Fall-related ED presentation	22 (22)
Admitted to a care supporting facility after 6 weeks of follow-up	
Yes	10 (10)
No	75 (75)
Lost to follow-up	15 (15)
*Medical specialty responsible for treatment plan. ED, emergency department.	

(table 1). Majority of the patients (74%) assessed their care situation at home as good. Thirty-four patients (34%) presenting to the ED were self-referrals, 42 patients (42%) were referred by a GP, and 24 patients (24%) were sent in by a medical specialist. Half of the patients (50%) were sent home after their ED presentation, 49 patients (49%) were admitted to the hospital, and 1 patient (1%) was discharged to an emergency respite placement in a nursing home. At 6-week follow-up, 10 patients (10%)

	Discharged home	Admitted	
	n=50	n=50	P value
Age, mean (range)	77 (70–92), SD 6.3	79 (70–96), SD 7.7	0.271
Sex, n (%)			0.841
Male	27 (54)	28 (56)	
Female	23 (46)	22 (44)	
Home care, n (%)			0.006
Yes	3 (6)	13 (26)	
No	47 (94)	37 (74)	
Polypharmacy*, n (%)			0.221
Yes	23 (46)	32 (64)	
No	27 (54)	18 (36)	
APOP decline, mean (range) ¹⁵	23.18 (0–70), SD 14.17	33.48 (8–80), SD 20.98	0.005
APOP mortality, mean (range) ¹⁵	4.96 (0–21), SD 4.281	9.72 (0–37), SD 8.86	0.001
Type of referral, n (%)			0.717
Self-referral	18 (36)	16 (32)	
GP	19 (38)	23 (46)	
Specialist	13 (26)	11 (22)	
Arrival by ambulance, n (%)			0.069
Yes	17 (34)	26 (52)	
No	33 (66)	24 (48)	
Triage code, to be seen, n (%)			0.028
U1: direct	0 (0)	5 (10)	
U2: <10 min	16 (32)	25 (50)	
U3: >10 min	20 (40)	13 (26)	
U4: >1 hour	5 (10)	2 (4)	
U5: >1 hour	9 (18)	5 (10)	
Deceased at 6-week follow-up, n (%)			0.881
Yes	4 (8)	3 (6)	
No	42 (84)	42 (84)	
Lost to follow-up	4 (8)	5 (10)	

*Polypharmacy: medication use ≥5.

APOP, acute presenting older patient; GP, general practitioner.

were admitted to a care supporting facility and 7 patients (7%) were deceased.

Patients discharged home versus admitted patients

Significant differences were found in home care, APOP score and triage code; patients admitted to the hospital or a nursing home received more home care (n=13 (26%)) vs n=3 (6%), p=0.006) and were more frequently triaged to be seen within 10min (n=30 (60%) vs n=16 (32%), p=0.028). Furthermore, patients admitted to the hospital or a nursing home had a higher risk of functional decline and mortality in the next 3 months according to the APOP score (table 2).

PRISMA analysis and root causes

The PRISMA method identified 159 root causes that contributed to ED presentation of the 100 patients

studied. In more than half of the patients (54%) a single root cause was identified, 36 patients (36%) had two root causes, 8 patients (8%) had three root causes, and 2 patients (2%) had four or more root causes. The categories, descriptions, examples based on our study population and the frequencies of all root causes are displayed in table 3.

Majority (n=121, 76%) of the root causes were related to the individual specifics of the patient and could be divided into disease-related factors (n=93, 58.5%) and patient-related factors (n=28, 17.6%). Disease-related factors, such as progression of a malignant tumour or exacerbation of chronic obstructive pulmonary disease, were mostly beyond the control of the patient and the physician. Patient-related causes, such as refusal to take

Table 3 Desc	ription of categorie	s of the E	Description of categories of the Eindhoven Classification Model: PRISMA medical version	cal version		
Main category	Subcategory	Code	Description	L Examples (if available)	Discharged home frequencies n (%)*	Admitted frequencies n (%)*
Technical	External	T-ex	Technical failures beyond the control of the organisation.	Not available.	0 (0)	(0) 0
	Design	D	Failures due to poor design of equipment, etc.	Not available.	0 (0)	0 (0)
	Construction	5	Correct design inappropriately constructed or placed.	Not available.	0 (0)	(0) 0
	Materials	TM	Material defects not classified under TD or TC.	Not available.	0 (0)	0 (0)
Organisational	External	O-ex	Failures at an organisational level beyond the control and responsibility of the investigating team.	Patient presented to the ED due to delay in time to operate due to delay in receiving patient information from an external hospital.	0) 0	1 (1.4)
	Transfer of knowledge	Хo	Failure resulting from inadequate measures to train or supervise new or inexperienced staff.	Not available.	0 (0)	(0) 0
	Protocols	ОР	Failures relating to the quality or availability of appropriate protocols.	Oncological patient who is instructed by the specialist to present to the ED when he has fever.	1 (1.2%)	2 (2.7)
	Management priorities	WO	Internal management decisions which reduce focus on patient safety when faced with conflicting priorities.	Patient presented to the ED because there is no short-term outpatient department appointment available. Presentation due to long waiting time until operation.	7 (8.2)	5 (6.7)
	Culture	00	Failure due to attitude and approach of the treating organisation.	Patient is sent from the outpatient department to the ED by a specialist instead of to the GP.	1 (1.2)	1 (1.4)
Human	External	H-ex	Human failures beyond the control of the organisation/department.	Patient arrived at the ED with an ambulance, which was called by bystanders after a fall on the street.	1 (1.2)	(0) 0
	Knowledge-based behaviour	HKK	Failure of an individual to apply their knowledge to a new clinical situation.	GP thought the fever was due to influenza instead of rheumatism. Therefore inadequate treatment and presentation to ED.	1 (1.2)	2 (2.7)
	Qualifications	НКО	An inappropriately trained individual performing the clinical task.	Not available.	0 (0)	(0) 0
	Coordination	HRC	A lack of task coordination within the healthcare team.	Not available.	0 (0)	(0) 0
	Verification	HRV	Failure to correctly check and assess the situation before performing interventions	GP refers the patient to the ED directly without examining the patient adequately due to lack of time.	3 (1.9)	(0) 0
	Intervention	HRI	Failure resulting from faulty task planning or performance.	Inadequate medication schedule, therefore progression of complaints. Inadequate explanation to the patient when to present to the ED.	4 (4.7)	3 (4.0)
	Monitoring	HRM	Failure to monitor the patient's progress or condition.	Patient was admitted to the hospital, no adequate analysis of complaints and discharged home. Presents to the ED with same complaints. Insufficient monitoring done by GP.	1 (1.2)	1 (1.4)
	Skills-based	HSS	Failure in performance of highly developed skills.	Not available.	0 (0)	0 (0)
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Table 3 Continued	inued					
Main category Subcategory	Subcategory	Code	Description	Examples (if available)	Discharged home frequencies n (%)*	Admitted frequencies n (%)*
Patient	Patient-related	PRF	Failures related to patient characteristics or conditions, which are beyond the control of staff and influence clinical progress.	Patient falls due to refusal to walk with walking aid. Patient postponed GP appointment due to anxiety and presents to ED with heavy complaints.	18 (21.2)	10 (13.5)
	Disease-related	DRF	Failures related to the natural progress of disease which are beyond the control of the patient, its carers and staff.	Patient with COPD presents with acute progression of 46 (54.1) dyspnoea. Shoulder luxation after fall.	- 46 (54.1)	47 (63.5)
×	Unclassifiable	×		Trauma capitis due to fall of suitcase during flight. Patient is still living independently despite frailty. Uncertainty of GP resulting in referral to ED. Patient presents to ED with postoperative infection.	2 (2.3)	2 (2.7)
Total					85 (100)	74 (100)
Distribution of 159 root o *Number of root causes. COPD, chronic obstructi	Distribution of 159 root causes based on 100 patient cases. 'Number of root causes. COPD, chronic obstructive pulmonary disease; ED, emerger	on 100 patie disease; ED,	nt cases. emergency department; GP, general practitioner; PRI	Distribution of 159 root causes based on 100 patient cases. 'Number of root causes. COPD, chronic obstructive pulmonary disease; ED, emergency department; GP, general practitioner; PRISMA, Prevention and Recovery Information System for Monitoring and Analysis.	onitoring and Analysis.	

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medication or to visit the GP before presenting to the ED, clearly influenced clinical progress but were beyond the control of healthcare workers. In 12 (7.5%) instances the root causes were organisational, for example a patient being unable to contact the GP by phone or arrange an early outpatient department appointment.

Preventability

Sixty-eight ED presentations were considered potentially preventable by either the patient, the physician at the ED or the patient's GP. Ten (10%) presentations were judged potentially preventable by the patient, 23 (23%) by the physician at the ED and 21 (21%) by the patient's GP (table 4).

In only four cases did the patient, the attending physi-9 cian at the ED and the patient's GP all agree that the ED 8 presentation could, potentially, have been prevented. One patient could have visited the GP earlier, but tried to ignore his complaints due to anxiety. A patient with a back injury after a fall found it too difficult to arrange a GP appointment. Another patient with epistaxis went straight to the ED because he thought the GP would not be able to help him, and a patient with known allergies developed a reaction to antibiotics that should not have uses related to been prescribed. In these four agreed cases, preventability was based on patient-related, organisational or human verification causes.

DISCUSSION

The main finding of this study is that the most common root causes contributing to ED presentations in older patients are disease-related (59%), followed by patientrelated causes (18%). In addition, there was little consensus between patients, physicians at the ED and GPs on the preventability of an ED presentation.

Disease-related factors are associated with progression or development of a new manifestation of an existing illness. Although in this study both patients and physicians felt most of these presentations were not potentially preventable, this may not always be the case. For example, a patient with a problem based on a disease-related factor could, in some cases, also have been treated by their GP without referral to the ED. Moreover, if patients are discharged home after an ED presentation, this does not necessarily mean that the presentation was inappropriate and therefore preventable. For example, an ED presentation might identify a urinary tract infection as the cause of a fall and X-rays confirm no fractures had occurred, which would allow treatment with antibiotics to continue in the patient's home.

Others have reported similar results to this study. A recent study of Verhaegh *et al*¹⁷ found that patients and caregivers considered an ED presentation preventable less frequently than professionals (patients 12.2%, GPs 20.7%, physicians at ED 31.2%). Suffoletto *et al*¹⁸ also reported little agreement on preventability between patients and healthcare professionals. There is no consensus definition of a preventable ED presentation as it depends on the different perspectives of the patients, their GP and the

Preventability Patient	Yes, n (%)	No, n (%)	Don't know, n (%)	Missing, n (%)	P value 0.182
Discharged home	7 (14)	43 (86)	0 (0)	0 (0)	0.102
Admitted	3 (6)	47 (94)	0 (0)	0 (0)	
Physician at the emergency department					0.616
Discharged home	14 (28)	27 (54)	1 (2)	8 (16)	
Admitted	9 (18)	24 (48)	2 (4)	15 (30)	
General practitioner					0.010
Discharged home	16 (34)	30 (60)	0 (0)	4 (6)	
Admitted	5 (10)	34 (68)	0 (0)	11 (22)	

attending physician at the ED. In this study 42 patients were referred to the hospital by their GP, and in this group the GP judged the ED presentation potentially preventable in just 8 cases (19%). From any physician's perspective, any presentation that could be managed in an alternative setting could be considered potentially preventable. Likewise, if a patient is a self-referral to the ED, it is likely that he/she will judge the ED presentation as not preventable. Although 34 patients were self-referrals, only 4 of them (12%) judged the ED presentation as potentially preventable. It is possible, of course, that more patients would concede that their presentation was preventable had they been better informed on alternative treatment options, and these were convenient and easily available. Overall, physicians at the ED judged that 23% of the presentations were potentially preventable. This suggests they believe that these patients could have been managed effectively by other health service providers, such as patients triaged as low urgency (triage code U4 and U5, they can be seen after 1 hour). Our results show that patients admitted to the hospital had a significantly high urgency triage code. Patients with a low urgency code could have been seen at their GP instead of the ED, which would allow the ED to focus more on emergency and urgent presentations.

New solutions should be explored to ensure that the acute care pathway remains accessible and available and care is of sufficient quality for the increasing number of older patients.^{7 19 20} Ĥalf of the patients in this study were admitted to the hospital. Prior to ED presentations, these patients had a higher APOP decline and mortality score and a higher triage score. Nevertheless, there was no significant difference in the root cause profile and the number of deceased patients at 6-month follow-up between these patients and the remaining 50% of patients who were not admitted to the hospital. A presentation of older patients to the ED therefore is associated with negative outcomes regardless of the need of immediate hospitalisation. The older patient population accounts for a large proportion of ED presentations, and the contemporary emergency medicine model, including policies and procedures, processes and physical design, may not be adequate for their needs.^{19 20} It is vital that an ED recognises the

importance of fostering an age-friendly environment so that acute care for older patients is optimal. This can be achieved through the introduction of care pathways that include consultations with geriatric nurses^{21 22} or an ED observation unit for older patients.²³ The geographical Бu design of the ED and training healthcare professionals ġ in the management of common geriatric syndromes^{7 21 22} uses should be improved.

For future research, changes in the acute care pathways of older patients are needed to improve their care by providing alternatives to ED presentations, such as high urgency outpatient department²⁴ or the introduction of advanced care planning.²⁵ Furthermore, it would be interesting to see whether some causes are tied to perceived preventability more than others and to include other healthcare workers in the analysis of root causes.

Strengths

A major strength of our study is the inclusion of patients' ģ perspectives. Understanding patients' perspectives is needed to design strategies that create a more compretraining hensive, patient-centred approach to older patients who present to the ED. We determined the causal factors by using the PRISMA method, which, compared with other methods, efficiently examines the active (ie, human failures) and latent (ie, technical and organisational failures) factors to identify reoccurring patterns of root causes.¹²¹³

Limitations This study has some limitations. First, although the PRISMA method is highly structured and accepted by the World Alliance for Patient Safety by the WHO,^{12 13} it is relatively **g**. new and has not been used in this setting before. The **8** causal trees of some patients may be incomplete due to missing responses. We only included patients in a selected period during peak hours. Furthermore, our study population excluded patients who were likely to be frail, such as those living in an assisted living facility or nursing home and patients with inability to sign informed consent due to delirium or other cognitive impairments. Finally, the study was performed in one Dutch hospital, so our findings may not be applicable to other hospitals or countries.

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CONCLUSION

It is important to improve the quality of care and safety for older patients within the acute care pathway. In this study the root causes of most ED presentations in older patients were related to their disease, and there is little agreement between patients and healthcare workers on ED presentations that were potentially preventable. To prevent ED presentations of older patients, new solutions that focus on providing alternative settings within the acute care pathway are required.

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Contributors Study concept and design were performed by BD, HM and PWBN. Planning of the study was done by BD, HM and RB. Acquisition of data was done by BD, HM, RB and PWBN. BD, HM, RB and PWBN analysed the data, and BD, HM, RB, PWBN, CW and HJB interpreted the data. Statistical expertise was done by BD, HM and PWBN. BD made a draft of the manuscript. HM, RB, PWBN, CW and HJB gave feedback after critical revision of the manuscript for important intellectual content. BD, HM, RB, PWBN, CW and HJB read and approved the final manuscript.

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Data availability statement All data relevant to the study are included in the article or uploaded as supplemental information. The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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