To cite: Visade F. Babykina G.

Identifying specific subgroups

repeated hospital readmissions

Carretero-Bravo J, et al.

of older patients at risk of

and death after discharge

in a prospective multicentre

cohort in France. BMJ Open

bmjopen-2024-085004

Prepublication history

and additional supplemental

available online. To view these files, please visit the journal

online (https://doi.org/10.1136/

material for this paper are

bmjopen-2024-085004).

Received 02 February 2024

Accepted 12 December 2024

2025;15:e085004. doi:10.1136/

BMJ Open Identifying specific subgroups of older patients at risk of repeated hospital readmissions and death after discharge in a prospective multicentre cohort in France

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ABSTRACT

Objective To identify specific subgroups of older patients at risk of repeated hospital readmissions and death.

Design Prospective, multicentre, DAMAGE (Patient Outcomes After Hospitalization in Acute Geriatric Unit) cohort of adults aged 75 and over, discharged from an acute geriatric unit (AGU) and followed up for 12 months. Setting Six recruiting hospital centres in the Hauts-de-France and Normandie regions of France.

Main outcome measures We performed a latent class readmissions and death, followed by a logistic regression

Results 3081 patients were included (mean (SD) age: 86.4 (5.5)) and two subgroups were identified. In subgroup 1 (n=2169, 70.4%), only 619 (28.5%) patients were readmitted to hospital once during the follow-up, and 495 (22.5%) died. In subgroup 2 (n=912, 29.6%), all patients were readmitted to hospital at least twice, and 523 (57.8%) died. Subgroup 2 accounted for 29.6% of patients but 74.4% of hospital readmissions, with longer lengths of stay, and 51.6% of deaths. A multivariate logistic regression analysis identified only four characteristics weakly associated with the risk of being in subgroup 2 (at least one hospital admission in the 6 months preceding the index hospital admission, cancer, polymedication and weight changes (gain or loss) during the index hospital admission). The area under the receiver operating

population of older adults hospitalised in an AGU is divided into two subgroups with regard to the postdischarge outcomes: one subgroup (70% of the individuals) will have a low rate of hospital readmission and a moderate death rate, whereas the other will have a high rate of hospital readmission and a very high death rate. There is a need for predictive scores for both events, with a view to better targeting at-risk patients.

Trial registration number Trial registration number was approved by the local independent ethics committee (CPP Nord-Ouest IV, Lille, France) on 13 February 2015, with

STRENGTHS AND LIMITATIONS OF THIS STUDY

- \Rightarrow Use of high-guality data from a multicentre cohort.
- \Rightarrow Long follow-up (1 year).
- ⇒ Accounting for hospital readmissions as a recurrent events process using a specific statistical analysis adapted for such data.
- \Rightarrow Use of clustering to classify patients into a class increases the chances of having groups correlated with hospital readmissions and death.
- \Rightarrow The analysis was limited to older patients discharged from an acute geriatric unit.

an amendment approved on 21 January 2016 (reference: IDRCB 2014 A01670 47, CNIL bxA15352514).

INTRODUCTION

ģ Hospital readmission is frequent in older ≥ adults and is associated with greater morbidity training, and mortality, loss of autonomy and excessive healthcare costs.¹⁻⁴ Initiatives to reduce the risk of hospital readmission among older adults have had mixed results.⁵⁶ Most of these initiatives are based on the determination of clinical characteristics associated with the first hospital readmission (typically within a timerame ranging from 30 days to 12 months) the identification of at-risk older dults.³⁷⁸ Recent research results have shown that **g** frame ranging from 30 days to 12 months) and thus the identification of at-risk older adults.378

the hospital readmission process is not **3** limited to the first readmission; the process is dynamic, with each new hospital readmission increasing the risk of further readmissions within increasingly shorter timeframes. Moreover, the hospital readmission process is associated with the risk of death.⁹ Lastly, clinical characteristics do not account for much of the variability in the risk of multiple hospital readmissions.¹⁰ All these elements suggest that

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analysis to identify subgroups at risk of repeated hospital analysis to determine the characteristics associated with the identified subaroups.

characteristic curve was 63%. Conclusion A latent class analysis showed that a

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there is poorly explored, poorly explained heterogeneity in older adults' outcomes (ie, hospital readmission and death after the first readmission). In this context, it can be useful to identify within the whole heterogeneous population some subgroups, which are more homogeneous in terms of different characteristics (potential risk factors for repeated hospital admissions). The difficulty is that specific characteristics which determine these subgroups are often not directly observed, even though they depend on the observed patients' features. It is assumed that the subgroups are determined by some latent (not observed) variable, called latent class. The statistical tool, called latent class analysis, can be used to identify subgroups within a large but heterogeneous population.¹¹ Usefully, this approach does not require a priori knowledge or explanations in terms of clinical characteristics, but the identified subgroups (latent classes) can be characterised a posteriori by observed clinical characteristics. To the best of our knowledge, latent class analysis has not previously been used to study the heterogeneity of older adults with regard to the risk of repeat hospital readmissions and death after the first hospital readmission.

The objectives of the present study were to (1) identify specific subgroups of older patients at risk of repeat hospital readmissions and death after the initial hospital stay and (2) determine the associated characteristics.

METHODS

Study design

The DAMAGE study is a multicentre, prospective cohort study of patients aged 75 or over hospitalised in an acute geriatric unit (AGU) in the Hauts-de-France and Normandie regions of France (NCT02949635). The six recruiting centres are Lille University Hospital (Lille, France; two AGUs), Saint Philibert Hospital (Lille, France; one AGU), Amiens-Picardie University Hospital (Amiens, France; one AGU), Caen University Hospital (Caen, France; one AGU) and Saint Quentin General Hospital (Saint Quentin, France; one AGU). Patients discharged from the AGU to a non-acute facility (the patient's home, a residential home or a rehabilitation unit) were followed up for 1 year. The inclusion period ran from 14 September 2016 to 29 January 2018. The last 12-month follow-up visit was performed on 29 January 2019.

Inclusion and exclusion criteria

All patients aged 75 and over with health insurance coverage and hospitalised in an AGU were eligible for inclusion in the study. Patients hospitalised in the AGU for less than 48 hours were not included because this short duration prevented the completion of a comprehensive geriatric assessment. Patients admitted for immediate palliative care were not considered for inclusion in the study because of the high risk of death. Lastly, patients who refused to participate in the study (as notified by the patient or his/her primary family caregiver or legal

representative) were not included. However, cognitive impairment was not an exclusion criterion per se.

Patients who died in the AGU were excluded because one of the study's objectives concerned the assessment of the death rate after discharge. Patients transferred to another acute care ward (a surgical ward or a nongeriatric ward) without returning to the AGU were also excluded. Lastly, patients transferred to palliative care units or having received palliative care during the stay in the AGU were excluded because of the above-mentioned high risk of death.

Collection of data during the stay in the AGU

Protected by copyrigh Data were collected at various time points during the initial stay in the AGU using a case report form. The social, clinical and geriatric variables recorded within 72 hours of admission, during the hospital stay and on discharge are listed in online supplemental data 1.

- The social and clinical variables recorded on admission included the age, sex, type of home environment (own home or residential home), number of previous ßu hospital stays, the Charlson Comorbidity Index¹² and whether or not the patient had a diagnosis of cancer. The geriatric variables recorded on admission and whether or not the patient had a diagnosis of included the number of medications usually taken, dependency before hospital admission (the Katz Index of independence in activities of daily living
- dependency before hospital admission (the Katz Index of independence in activities of daily living (Katz ADL)).¹³ malnutrition (weight loss and the body mass index), cognitive disorders, any history of depression, swallowing disorders and walking ability. Standard laboratory variables were also recorded. During the hospital stay, a daily evaluation of clinical status enabled us to classify the patient into one of five predefined states: late discharge (defined by the doctor in charge as being medically fit for discharge but remain in the hospital for social or personal reasons,¹⁴ a medical obstacle to discharge (other than infection), treatment of a community-acquired infec-tion, treatment of a hospital-acquired infection and palliative care. These clinical states were mutually exclusive (ie, only one state per day and per patient) and were determined by the patient's attending physician. On the day of discharge, geriatric variables were also recorded: the patient's bodyweight, the bodyweight difference between admission and discharge destina-tion (the patient's won home, a residential home or a rehabilitation unit). The collected data were audited. Lastly, data collected during the hospital stay were used to calculate the 1-year mortality risk score (the DAMAGE score) developed in a previous study of the same cohort.¹⁴

Follow-up

The exact date of hospital readmission and the exact date of death (if applicable) were collected at 3 and 12 months after the index discharge from the AGU; this was done by phoning the patient (if alive), his/her next of kin or caregiver or the referring healthcare professional in a community setting (eg, the general practitioner). Patient mortality was also evaluated by consulting freely available national mortality data. The 12-month follow-up period corresponded to the main objective of the DAMAGE cohort, which sought to develop a prognostic score for 3- and 12-month mortality after discharge from an AGU, based on a comprehensive geriatric assessment, and in-hospital events.¹⁴

Statistical analysis

Categorical variables were expressed as the frequency (percentage). Continuous variables were expressed as the mean±SD if normally distributed or as the median (IOR) otherwise. Normal data distributions were checked graphically and by applying the Shapiro-Wilk test.

To identify homogeneous subgroups of patients in terms of the risk of repeated hospital admission, we performed a latent class analysis.¹⁵ This approach combines the wellknown Andersen-Gill model,¹⁶ which models the occurrence of recurrent events and has already been used to study hospital readmissions of older adults,^{9 10} with the mixture model,¹⁷ allowing to account for a mixture of distributions (distributions with different parameters). The probability of belonging to a so-called 'latent' class, that is, one not directly observed in the data, is a parameter estimated from observed data. Latent classes are constructed on the basis of the observed responses (hospital readmission) of cases (patients) on a set of indicator variables (observed and collected variables). Patients are assigned to classes with the highest probability of membership a posteriori (after the model parameters estimation), and the variables associated with the recurrence process in the Andersen-Gill model can be specific to these latent classes. This approach has the advantage of not requiring a priori knowledge of the classes or an explanation of the classes in terms of clinical characteristics. Death, on the other hand, is considered censorship.

The intergroup difference between the identified latent classes was assessed a posteriori in Student's t-test (for normally distributed data) or Wilcoxon's test (in all

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The overall procedures of the data analysis. AIC, Akaike information criterion. Figure 1

Table 1 Characteristics of the overall study population

	Study population (n=3081)	
	Ν	Value
Social and clinical characteristics		
Age, years (mean±SD)	3081	86.4±5.5
Sex (male), N (%)	3081	1050 (34.1)
Place of residence, N (%)	3077	
At home		2484 (80.7)
In a residential home		593 (19.2)
Hospitalised in the previous 6 months, N (%)	3028	1178 (38.9)
Charlson comorbidity index, N (%)	3081	
0–2		1295 (42)
3–4		1485 (48)
>4		300 (9.9)
Cancer, N (%)	3059	459 (15.0)
Geriatric syndromes		
Living alone, N (%)	3063	1412 (46.1)
Socially isolated, N (%)	3050	261 (8.6)
Number of medications taken at home (mean±SD)	3077	7.9±3.6
Polypharmacy*, N (%)	3026	655 (21.6)
Psychotropic medication, N (%)	3047	1679 (55.1)
Katz ADL at home†, N (%)	2905	
≥3		2217 (76.3)
< 3		688 (23.7)
Body mass index (mean±SD)	2800	25.1±5.7
Malnutrition‡, N (%)	2890	808 (28)
Swallowing disorder, N (%)	3023	449 (14.8)
History of depression, N (%)	3055	614 (20.1)
Cognitive disorder§, N (%)	3081	
No		1406 (45.6)
Memory complaints		566 (18.4)
Known neurocognitive disorders		1109 (36)
Walking ability, N (%)	3065	
No, confined to bed		151 (4.9)
No, bed or chair only		416 (13.6)
Walks with assistance		1412 (46.1)
Walks unaided		1086 (35.4)
Changes in hospital		
Katz ADL on admission (median (IQR))	3066	3.0 (1.0; 5.0)
Katz ADL on discharge (median (IQR))	3028	4.0 (2.0; 5.0)
Change in Katz ADL in hospital, N (%)	3024	
Worse		274 (9.1)
Stable		1699 (56.2)
Better		1051 (34.8)
Bodyweight on admission, kg (median (IQR))	2926	64.9 (55.0; 76.6)
Bodyweight on discharge, kg (median (IQR))	2225	64.0 (54.0; 76.0)
Change in bodyweight in hospital N (%)	2176	
- • •		

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Continued

Table 1

Continued

	Study population (n=3081)	
	N	Value
Decrease		1034 (47.5)
Stable		398 (18.3)
Increase		744 (34.2)
Serum albumin level, g/L (mean±SD)	3015	31.8±5.4
Blood haemoglobin level, g/L (mean±SD)	3075	11.7±1.9
Serum creatinine level, µmol/mL (median (IQR))	3075	87.5 (64.5; 114.9)
Delirium on admission, N (%)	3081	425 (13.8)
Time spent in each state during the hospital stay, days (mean \pm SD)	3081	
Late discharge¶		3.6±4.1
Medical obstacle to discharge**		5.3±4.7
Community-acquired infection		1.4±2.9
Hospital-acquired infection		0.3±1.7
Follow-up		
Number of hospital admissions during follow-up, N		2670
Patients readmitted to hospital, N (%)		1531 (49)
One hospital readmission		856 (19)
Two hospital readmissions		350 (11)
Three hospital readmissions		142 (4.6)
Four hospital readmissions		63 (2.0)
Five hospital readmissions		18 (0.5)
Death during follow-up, N (%)		1014 (32.9)

*At least 10 medications taken at home.

†Dependence before admission was defined as a Katz ADL score at home <3.

‡Weight loss >5% in 1 month or >10% in 6 months, or body mass index <21.

§Memory complaints reported by the family or the patient, or known neurocognitive disorders.

¶Late discharge, defined as being in a stable state for all 24 hours of the previous working day.

**Medical obstacle to discharge: assigned if the patient was not in any of the other states (late discharge, treatment of a community-acquired infection, treatment of a hospital-acquired infection or palliative care).

ADL, activities of daily living; N, number of patients with no missing data.

care unit. A total of 3112 patients met all the inclusion criteria and none of the exclusion criteria. 31 patients had hospital admission date errors during the follow-up period. Our analyses, therefore, covered a total of 3081 patients.

The general characteristics of the DAMAGE cohort (table 1) show that the population was very old (mean (SD) age: 86.4 (5.5)) and predominantly female (66%). Around a third of the patients were malnourished (28%) or had been diagnosed with a neurocognitive disorder (36%). At the end of the 1-year follow-up period, 1447 patients (47%) had been readmitted to the hospital: 856 patients had been readmitted (19%) only once, and 591 (28%) had been readmitted at least twice. A total of 1014 patients (32.9%) had died by the end of the follow-up period.

Patient outcomes at discharge from the AGU

The latent class analysis identified two subgroups within the DAMAGE cohort in terms of posthospitalisation

Protected by copyright, including for uses related to text and data mining, AI training, a outcomes (table 2). The difference was mainly related to the number of hospital readmissions. The vast majority of older adults in subgroup 1 (n=2169, 70.4%) were Ы not readmitted to hospital during follow-up, and a few <u>0</u> were readmitted but only once. In contrast, all the older adults in subgroup 2 (n=912, 29.6%) were readmitted to hospital at least twice during follow-up. The death rate was also 2.5 times higher in subgroup 2 than in subgroup 1. Subgroup 2 accounted for 29.6% of the overall population but 74.4% of hospital readmissions and 51.6% of deaths. The mean cumulative number of hospitalisations by subgroups 1 or 2, over the follow-up period, is summarised in figure 2. At the end of follow-up, patients in subgroup 2 had, on average, more than three hospital readmissions, while those in subgroup 1 had fewer than one.

The proportion (in %) of the total follow-up period spent in hospital was three times higher in subgroup 2 (median (IQR): 6.3% (3.6; 11.7)) than in subgroup 1

Patient outcomes by subgroup

Table 2 Tatlefit outcomes by subgroup			
Follow-up	Subgroup 1 (n=2169)	Subgroup 2 (n=912)	P value
Age, years (mean±SD)	86.5 (5.4)	86.3±5.5	
Sex (male), N (%)	707 (32.5%)	345 (37.8%)	
Number of hospital admissions during follow-up, N	619	2051	
Patients readmitted to hospital, N	619	912	<0.001
One hospital readmission	619 (100)	912 (100)	
Two hospital readmissions	0	608 (66.7)	
Three hospital readmissions	0	232 (25.4)	
Four hospital readmissions	0	95 (10.4)	
Five hospital readmissions	0	59 (6.5)	
Length of hospital stay, days (median (IQR))	8 (5; 14)	18 (10; 30)	<0.001
Proportion (%) of the total follow-up time spent in hospital (median (IQR))	2.2 (1.4; 4.1)	6.3 (3.6; 11.7)	<0.001
Length of hospital stay before death, day (median (IQR))	10 (5; 13)	15.5 (8; 29)	<0.001
Death during follow-up, N	491	523	<0.001
Patients readmitted to hospital before death, N (%)	37 (7.5)	523 (100)	<0.001

(median (IQR): 2.2% (1.4; 4.1)). Hospital stays were also significantly longer for subgroup 2 patients, with a median of 18 days (IQR: (10; 30)), compared with 8 days (IQR: (5; 14)) for subgroup 1 patients. Of the 523 patients who died in subgroup 2, all were readmitted to hospital before death, whereas a minority of the 491 patients who died in subgroup 1 (n=37, 7.5%) were readmitted to hospital during follow-up, before death.

Subgroup prediction based on variables

In a bivariate analysis, a total of 12 characteristics were associated with belonging to the most at-risk subgroup (online supplemental data 3). In the multivariate analysis, only four characteristics were independently associated with belonging to the most at-risk subgroup: at least one hospital admission in the 6 months preceding the index hospital admission, cancer, polymedication and weight changes (gain or loss) during the index hospital admission. The ORs associated with these characteristics were low and ranged from 1.05 to 1.63 (table 3). The area under the receiver operating characteristic (ROC) curve was 63% (online supplemental data 4). Bivariate analysis with the DAMAGE death risk score showed a weak association, with an OR 95% CI of 1.37 (1.22, 1.53).

DISCUSSION

Our results showed that older adults discharged from an AGU can be divided into two outcome categories. Barely 30% of patients accounted for more than two-thirds of future hospital readmissions and more than half of all deaths in the entire cohort. These patients had longer hospital stays and spent more time in hospital during the follow-up period.

Most studies of the posthospitalisation fate of older adults have been limited to either an analysis of the first

hospital readmission (within a timeframe ranging from 1 to 24 months)^{7 8 23 24} or the risk of death (within a timeframe ranging from 1 month to several years).^{25 26} These <u>6</u> approaches have clear limitations, such as inability to ated to deal with multiple hospital readmissions during follow-up or to take account of the link between hospital readmission and death.²³ The results of our latent class analysis confirmed that the outcomes in a population of older adults hospitalised in the AGU were heterogeneous. In subgroup 1, few older adults are readmitted to hospital, the death rate is 22% and most deaths occur without hospital readmission. This situation appears to correspond to the wishes expressed by older adults as to the preferred place of death (home).^{27 28} In contrast, the ٩ older adults in subgroup 2 were often readmitted to hospital-sometimes for longer periods-and had a death rate of 52% at the end of the study. This situation probably runs counter to the wishes of older adults with regard to the end of life. Furthermore, this situation may call into question the appropriateness of the use of healthcare resources for these patients: were all these hospital readmissions driven primarily by medically justified reasons, and in line with the patient's wishes? Would home care have been possible? In the case of progressive illnesses or multimorbidity, the wishes of older patients change, with a final preference for home care.²⁹ Multiple hospital readmission is a risk factor for fragmented care and inconsistent management of chronic diseases and is not necessarily chosen by older adults.^{29 30}

In order to adapt the care offered to patients and their carers, it would therefore be necessary to predict the risk of belonging to subgroup 2. In this respect, the results of our study are disappointing. While 40 distinct characteristics (including per-hospital events) were recorded in the DAMAGE study, all were only weakly associated





Figure 2 Graphical representation of the mean cumulative number of hospitalisations for each time point, by subgroups. The average number of cumulated hospitalisations is calculated over all individuals at risk at each time point. Hospital readmissions accumulate faster in subgroup 2 than in subgroup 1. Overall, patients in subgroup 2 had more hospital readmissions, on average, than those in subgroup 1.

with the risk of belonging to subgroup 2, and the area under the ROC curve was only 63%. The association with the DAMAGE death risk score was weak, even though the latter was developed specifically in this cohort. This is explained by the fact that 48.8% of the patients who died belonged to subgroup 1: the risk of death is not very discriminant for belonging to subgroup 1 versus subgroup 2. Several scores for predicting the risk of hospital readmission at 30 days have been developed.^{26 31} These scores effectively predict the occurrence of a new hospital admission³² and identify the patients most at risk of failure to return home.³³ However, our study showed that 42.7% of the patients readmitted to hospital belong to subgroup 1. These older adults will only be readmitted to hospital once over 12 months and are very unlikely to die during that period of time. The risk of the first hospital readmission is therefore of little significance in determining whether a patient belongs to subgroup 1 or subgroup 2. All in all, our results call for a change in the objectives

of these scores, and a move beyond the separate, exclu-**g** and similar technologies or 'death'. Our results also suggest that work is needed to identify the characteristics more strongly associated with the risk of multiple hospital readmissions and death (subgroup 2). In older patients, a multitude of factors other than clinical characteristics come into play: support for caregivers,³⁴ optimised care provision on discharge from the hospital etc.³⁵ The main strengths of our work are as follows: the use of high-quality data from a multicentre cohort of ACT

The main strengths of our work are as follows: the use of high-quality data from a multicentre cohort of AGU patients; a low proportion of missing data (often less than 5%); novelty, as (to the best of our knowledge) the first multicentre studies of older adults admitted to an AGU and with a standardised geriatric assessment; the small number of exclusion criteria and the use of latent class analysis, which had not previously been applied in studies of multiple hospital readmissions and death at discharge from an AGU. This analysis uses a specific statistical

	OR	95% CI	
Social and clinical characteristics			
Age (years)			
74–89	Reference	_	
90–104	1.07	(0.85, 1.35)	
Sex (female)	0.81	(0.66, 1.01)	
Place of residence			
At home	Reference	_	
In a residential home	0.83	(0.61, 1.13)	
Hospitalised in the previous 6 months	1.25	(1.15, 1.36)	
Cancer (present)	1.46	(1.11, 1.93)	
Geriatric syndromes			
Malnutrition	1.29	(0.95, 1.74)	
Swallowing disorder	1.21	(0.88, 1.66)	
Katz ADL at home			
≥ 3	Reference	_	
< 3	0.93	(0.85, 1.02)	
Polypharmacy	1.05	(1.02, 1.08)	
Cognitive disorder			
No	Reference	_	
Known neurocognitive disorders	0.94	(0.75, 1.21)	
Walking ability			
Walks unaided	Reference	-	
Walks with assistance	1.07	(0.84, 1.37)	
No, confined to bed	1.39	(071, 2.69)	
No, bed or chair only	1.02	(0.68, 1.52)	
Socially isolated	1.23	(0.85, 1.77)	
Changes in hospital			
Change in bodyweight in hospital			
Stable	Reference	_	
Decrease	1.44	(1.08, 1.94)	
Increase	1.63	(1.21, 2.22)	
Change in Katz ADL in hospital			
Stable	Reference	-	
Worse	1.28	(0.88, 1.84)	
Better	1.04	(0.84, 1.31)	

model, suitable for tracking recurrent events such as hospital readmissions. It therefore provides a methodology adapted to and in line with clinical intuitions in order to reliably model the reality of patients' repeated hospital readmissions.³⁶ Similarly, the use of a mixture model to classify patients into a class that is not directly observed in the data, but is estimated from the data, draws a direct parallel with the intuition that an experienced clinician may draw when faced with a patient at the end of life and at high risk of repeated hospitalisations. The

of having groups correlated with hospital readmissions, whereas classifying on the basis of independent variables would risk producing groups less relevant to the hospital readmission process.

Our study had several limitations. First, the older patients in our cohort were discharged from an AGU and were most often very old, with multiple comorbidities. Hence, our results cannot be extrapolated to the population of older adults as a whole, nor to patients

transferred to a medical department other than the AGU before discharge, which did not prevent them from being readmitted at a later date. Second, the case report form was initially filled in manually and then recoded electronically for statistical analysis. This may have led to data entry errors. Lastly, the latent classes identified here might be specific to the population of older patients in the DAMAGE cohort and might not be found among all older patients discharged from an AGU. However, the number of older patients in the DAMAGE cohort was large (over 3000).

CONCLUSION

Our results showed that older adults discharged from an AGU can be divided into two outcome categories. On one hand, some patients accounted for more than a third of hospital readmissions, more than half of the deaths and the longest hospital stays. On the other, some patients were never or rarely readmitted to hospital and were unlikely to die. There is a need for predictive scores for both events, with a view to better targeting at-risk patients.

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Acknowledgements The authors would like to thank all the centres participating in the DAMAGE cohort.

Contributors FV: conception, statistical analysis, writing and editing. GB: statistical analysis, critical review and editing. JC-B: statistical analysis, critical review and editing. GD: conception, critical review and editing. W: statistical analysis, critical review and editing. J-BB: conception, statistical analysis, writing and editing. FV is responsible for the overall content as the guarantor. All authors contributed to the final draft of the manuscript.

Funding This work was supported by the French government's inter-regional hospital-based clinical research program (reference: PHRC I 13-097).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval The DAMAGE study was conducted in compliance with the terms of the Declaration of Helsinki and was approved by the local independent ethics committee (CPP Nord-Ouest IV, Lille, France) on 13 February 2015 with an amendment approved on 21 January 2016 (reference: IDRCB 2014 A01670 47, CNIL bxA15352514). The patients and their primary family caregivers or legal representatives were given detailed verbal and written information about the study, in order to ensure that the patients fully understood the potential risks and benefits of participation. In accordance with the French legislation on observational, non-interventional studies of routine clinical care, written consent was not required. The patients were informed that they could refuse to participate in the study and that refusal would not have any impact on their treatment in the AGU. If the patient was potentially unable to state his/her refusal to participate in the DAMAGE study, the next of kin or legal representative could refuse participation.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The data are available upon request to the corresponding author.

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