

## Association between hospitalization and change of frailty status in the GAZEL cohort

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### Abstract

**OBJECTIVES:** To assess the relationship between changes of frailty status and intervening hospitalizations, using information of the GAZEL cohort, matched with the data of the French National Health Data System.

**RESEARCH DESIGN:** Observational cohort study.

**SUBJECTS:** Community-dwelling adults of the GAZEL cohort (n = 12145; aged between 58 and 75 years).

**MEASURES:** Frailty was determined with the Strawbridge questionnaire in 2012, 2013 and 2014. Data regarding hospitalizations (notably their number, length of stay, emergency department use, and main diagnosis) were collected from the French National Health Data System. The relationship between intervening hospitalizations and changes of frailty status over time was assessed with multivariate Markov models.

**RESULTS:** The prevalence of frailty was 14% in 2012 and 2013 and 17% in 2014. A total of 2715 changes in frailty status were observed from 2012 to 2014. At least one hospitalization was recorded for 1453 people (12%) between the 2012 and 2013 questionnaires, and 1472 (13%) between the 2013 and 2014 questionnaires. No association was found between intervening hospitalizations and changes of frailty status (aHR: 1.14 [0.97-1.35] for robust to frail transition and aHR: 0.89 [0.73-1.08] for frail to non-frail transition). However, repeated hospitalizations, hospitalizations after emergency department use, surgery and several diagnosis groups were significantly associated with transitions towards frailty or its recovery.

CONCLUSIONS: Hospitalizations encompass a wide range of clinical situations, some of them being associated with incident frailty. An early recognition of these situations could help to better prevent and manage frailty in the early old age.

Key words: frailty; hospitalization; transition; cohort; aging

## Introduction

Frailty is defined as a syndrome of decreased physiological reserves, causing vulnerability to adverse outcomes<sup>1</sup>. Two main conceptual frameworks of frailty exist: the frailty phenotype defined by Fried et al<sup>1</sup> and the index of deficit accumulation defined by Rockwood et al<sup>2</sup>. In addition, a number of other definitions and tools have been developed to assess frailty, in line with an increased attention of the medical community regarding the early management of health and functional decline among the elderly. Indeed, frailty often precedes disability; early identification of frailty can hence help to prevent and delay functional impairments<sup>3,4</sup>. Epidemiological studies highlighted factors associated with transitions towards frailty among robust people, as well as transitions towards recovery among frail people<sup>5-9</sup>. Some are constitutive and non-modifiable, such as age and gender, whereas others may be accessible to prevention and health policies, namely health disorders, lifestyle, social network, and healthcare system organization and use<sup>5-9</sup>. However, little is known about acute precipitants of frailty.

Although hospitalizations stand among the potential consequences of frailty<sup>10,11</sup>, it may also constitute a precipitating factor for incident frailty<sup>6,7</sup>. Previous studies demonstrated the negative impact of hospitalizations on functional capacities<sup>12-14</sup>. To our knowledge, 2 studies investigated the relationship between hospitalizations and the dynamics of the frailty phenotype. Gill and al.<sup>7</sup> assessed frailty every 18 months for 108 months among 754 North American people aged 70 years or older. They showed that intervening hospitalizations restrained recovery from pre-frail and frail states. Lee et al.<sup>6</sup> assessed the Fried's frailty status among 3018 Chinese, aged 65 or older, twice at 2 years of interval. In these studies, intervening hospitalizations were significantly associated with a worsening of the frailty status and, for women, associated with impeded recovery. However these studies did not stratify the risk according to the characteristics of the hospitalizations, notably the reason for hospitalization, the duration or whether it was planned or not. Hospitalizations include a wide range of clinical

situations, from minor life accident to vital emergencies. Taking into account detailed information about hospitalizations may help to further understand the role of hospitalizations in the frailty trajectories.

This study aimed to assess the relationship between changes in frailty status and intervening hospitalizations, using information of a prospective cohort, matched with the data of the French National Health Data System.

## **Methods**

### **Study design and participants**

This study was nested in the GAZEL cohort. Details regarding the study design have been described elsewhere<sup>15</sup>. Briefly, in 1989, 20625 employees (5614 women and 15011 men aged 35-50 years) of the French national electricity and gas utility (Electricité de France - Gaz de France, EDF-GDF) accepted to participate. Every year, participants were invited to complete a postal questionnaire including a large set of items dealing with health status, lifestyle, socioeconomic and occupational factors. Data were also collected from national registers and personal and medical departments of EDF-GDF. Our study population included subjects for whom at least 2 consecutive measures of frailty were available between 2012 and 2014. Ages ranged from 58 to 73 years old. Among the 13104 participants who answered to at least 1 questionnaire over the study period, 124 (1.0%) were excluded because they returned only 1 questionnaire, 198 (1.5%) because the 2 measures were not consecutive, and 377 (2.9%) because of missing data about frailty. The study sample finally included 12405 (95%) individuals, with 3 measures of frailty for 11218 (90%) of them and 2 for 1187 (10%) of them.

## Frailty assessment

Frailty was assessed according to the questionnaire established by Strawbridge et al. <sup>16</sup>. Four domains were assessed through 16 items:

- four items assessed the physical domain (sudden loss of balance, weakness in the arms, weakness in the legs, becoming dizzy when standing up quickly);
- two items assessed the nutritive domain (unexplained weight loss, loss of appetite);
- four items assessed the cognitive domain (difficulty paying attention, difficulty finding the right word, difficulty remembering things, forgetting where things were put);
- six items assessed the sensory domain (difficulty reading newspapers, difficulty recognizing a friend across the street, difficulty reading signs at night, hearing over the phone, hearing a normal conversation, hearing a conversation in a noisy room).

Scores for the last 6 items ranged from 1 to 4, with 1 = no difficulty, to 4 = great deal of difficulty. Scores for the first 10 items were rated differently, with 1 = rarely or never had the problem in the last 12 months, to 4 = very often had the problem. Participants who scored 3 or 4 in at least 1 item were considered to have difficulty in the corresponding domain. Subjects were considered frail if they reported difficulty in 2 domains or more and robust otherwise (0 or 1). In case of missing data regarding items of the Strawbridge questionnaire, individuals were included in the analysis if available information enabled to classify them as frail (at least 2 impaired domains) (n = 122, 2.3% of all frail) or non-frail (absence of impairment in at least 3 domains) (n = 91, 0.3% of all robust). Otherwise, they were excluded (n=576, 4.4% of all participants).

## Hospitalizations

The French National Health Data System comprises exhaustive data about the use of health care resources<sup>17</sup> for 100% of the study sample (excluding non-reimbursed care such as over-the-counter drugs), as well as information about hospitalizations in private and public hospitals. We extracted data from 2012 to 2014 about stays in medicine and surgery wards (excluding stays in rehabilitation and psychiatric wards). Participants were considered hospitalized if they stayed at least 1 night at the hospital. The following information about hospitalizations was used in the analysis:

- number of hospitalizations that occurred between 2 consecutive questionnaires;
- length of stay, dichotomized according to the median;
- severity according to a 4-level complications and comorbid conditions scale as defined in the French Diagnosis-Related-Groups (DRG) system<sup>18</sup> (1 = lowest to 4 = highest severity), dichotomized as low (grade 1-2) and high (grade 3-4) severity;
- major primary diagnosis category according to the 10th international disease classification (ICD-10);
- emergency department use;
- surgical act according to the French DRG system.

In case of multiple hospitalizations, the highest value was retained for length of stay and severity. Sensitive analysis was conducted using the cumulative length of stay during the study period.

## Covariates

Information about socio-demographic characteristics, behaviors, and health status was collected. Social situation was self-rated in 2013 using an 8-level Likert scale. A 3-level variable was created, corresponding to disadvantaged, intermediate, and comfortable social status. Family situation was defined as 'couple' if the participant was married or living with someone and 'alone' if separated, divorced, widowed or living alone. Underweight, normal and overweight groups were based on the body mass index (BMI) (underweight if  $BMI \leq 23 \text{ Kg/m}^2$  for males and  $21 \text{ Kg/m}^2$  for female and, overweight if  $BMI > 27 \text{ Kg/m}^2$  for both males and females). Polypharmacy was assessed using data of reimbursement of the National Health Data System. A 3-level variable was created to define polypharmacy according to the mean number of drugs consumed per 3-month periods during the year preceding the questionnaire<sup>19</sup>: no polypharmacy (0 to 4 drugs), moderate polypharmacy (5 to 9 drugs), and high polypharmacy (10 drugs or more). Seven self-reported diseases were considered: cancer, diabetes, high blood pressure, lung disease, heart disease, stroke and muscular or joint pain. A 3-level variable was defined<sup>20</sup>, depending on the number of self-reported diseases: 0/1/2 or more. Mental health was assessed through self-reported history of depression during the last 12 months.

## Statistical analysis

We used prevalence to describe categorical variables and mean +/- standard deviation (SD) for continuous variables. Association between hospitalizations and changes of frailty status were assessed using Markov multi-state models. Different multi-state models were run separately to evaluate the association with each characteristic of the hospitalizations. These models assumed time-homogenous intensities of transitions and, that future evolution depended on the current state. The state-transition matrix was set as a reversible robust-frail model. Transitions to death were disregarded due to low mortality (n=363; 2.8%). The variables introduced in the model



were chosen a priori and were the same for all the transitions considered by the model. Time-dependent covariates were assumed constant in between the times they were observed.

We reported results with adjusted hazard ratio (aHR) and 95% confidence intervals (95%CI). Analyses were performed using R software, version 3.4.1. and 'msm' package<sup>21</sup>.

## Results

### Population

The study population was mostly composed of males (74%). Mean age was 67 ( $\pm$  3.5) years in 2012 and ranged from 58 to 73 years. The prevalence of frailty varied between 14 and 17%, depending on the year considered. The most commonly impaired dimension was the sensory one; the least frequently impaired was the nutritional one. Most individuals (>80%) reported at least 1 health problem (Table 1).

### Hospitalizations

In the first inter-questionnaires period (2012-2013), 1453 (12%) people were hospitalized, and 1472 (13%) during the second period (2013-2014). The median length of stay was of 4 days with a majority of low severity diagnoses (86% and 83% of grade 1 or 2 severity, for the first and the second period respectively). Between 22 and 24% of the participants who were hospitalized used the emergency department, depending on the period considered. Nearly 60% of the participants who were hospitalized received surgery. The most frequent diagnoses were related to the circulatory system (I00-I99) (20% of hospitalized individuals in both periods), followed by cancer (C00-D48) (18%), and musculoskeletal system and connective tissue diseases (M00-M99) (16% and 17% respectively). Characteristics of the hospitalizations are further described in Table 2.

## Frailty transitions

During the follow-up, 23623 consecutive measures of frailty were available; they included 2715 (12%) changes of frailty status. The most frequent transition was from the robust to the frail state (n=1519, 7.5%).

Crude hazards of change of the frailty status were significantly different between individuals who were hospitalized and those who were not (HRa: 1.41 [1.22; 1.63] for robust to frail transition and HRa: 0.77 [0.65; 0.91] for frail to robust transition), but not in multivariate analysis (Table 3). However, those who were hospitalized multiple times were more likely to become frail (R-F transition) (HRa: 1.32 [1.01 – 1.74]). Hospitalizations involving the use of the emergency department were also associated with R-F transition (HRa: 1.38 [1.03 – 1.85]), as well as hospitalizations without surgery (HRa: 1.36 [1.08 – 1.73]), high severity conditions (HRa: 1.50 [1.05 – 2.15]) and groups of diagnoses ‘Symptoms, signs & abnormal clinical & laboratory findings, not elsewhere classified’ (HRa: 1.70 [1.01 – 2.86]) and ‘Factors influencing health status & contact with health services’ (HRa: 1.51 [1.06 – 2.14]) (Table 4). The group ‘Symptoms, signs & abnormal clinical & laboratory findings, not elsewhere classified’ mainly consisted in urinary retention, syncope and collapse, and unspecified chest pain, whereas ‘Factors influencing health status & contact with health services’ mainly included dialysis, chemotherapy, and polysomnography. The other factors associated with frailty transitions were older age, polypharmacy, comorbidity, and depression. A comfortable social status was associated with a lower risk of becoming frail.

On the other hand, some types of hospitalizations were negatively associated with recovery from frailty (F-R transition): hospitalizations involving surgery (HRa: 0.74 [0.56 – 0.96]) and hospitalizations due to ‘musculoskeletal system & connective tissue’ diseases (HRa: 0.59 [0.36 – 0.96]), a group of diagnosis that included arthrosis (coxarthrosis and gonarthrosis) and rotator

cuff syndrome. Other factors lowering the chances of recovery from frailty were older age, low BMI, polypharmacy, and depression.

We did not find any association between the length of stay and changes of frailty status.

## **Discussion**

### **Main results**

In a French cohort of 12405 individuals aged 58 and over, followed from 2012 to 2014, we found no association between changes of frailty status according to the Strawbridge's definition and intervening hospitalizations when all hospitalizations were considered together. However, we found that hospitalizations were significantly associated with changes of frailty status in particular settings, being multiple hospitalizations, use of emergency department and hospitalizations because of 2 diagnoses groups related to heterogeneous and chronic diseases.

### **Frailty and hospitalizations**

In line with previous prevalence found in studies by Strawbridge et al<sup>16</sup> and Matthews et al<sup>22</sup>, the prevalence of frailty varied from 14% in 2012 and 17% in 2014 in this population composed, by construction, of 74% of men. To our knowledge, this is the first time frailty transitions are studied using a multidimensional definition of frailty. As defined, we show that frailty is a transient state, consistently with the findings of studies using the frailty phenotype<sup>6,7</sup>. Indeed, more than 1/3 of frail individuals recovered from frailty during the follow-up.

Hospitalizations were described using the National Health Data System. Hospitalization prevalence and the main reasons for hospitalizations were consistent with national statistics

reported by the French Technical Agency for Information on Hospitalization ('Agence Technique de l'Information sur l'Hospitalisation')<sup>23</sup>.

### **Changes of frailty status and hospitalizations**

Previous studies<sup>6,7</sup> suggested an association between all-kind hospitalization and frailty transitions, whereas we did not confirm this result. Nevertheless, the extent of the comparison is limited by the use of different definitions to assess frailty, with on the one hand the multidimensional definition by Strawbridge et al, and on the other hand the physical frailty phenotype. One may hypothesized that a multidimensional approach of frailty is less sensitive than a physical definition regarding to the impact of hospitalization. However, a higher risk of transition towards frailty was observed in the case of multiple hospitalizations, in line with previous studies.

We showed that hospitalization in emergency was associated with incident frailty, in accordance with the hypothesis that hospitalization in emergency is more stressful than planned hospitalization. It may also reflect a difficulty for general practitioner to manage individuals at the edge of frailty. Surprisingly, we found that hospitalization without surgery was associated with an increased risk of transition towards frailty. This result may actually reflect the association between the use of the emergency department and incident frailty, as hospitalization without surgery and the use of the emergency department were hospitalizations' features, strongly related to each other. Indeed, surgery was less frequent among people who were admitted through the emergency department (36% vs 67% in the first period and 38% vs 66% in the second period; p-value < 10<sup>-3</sup>).

This study did not enable to highlight specific diagnoses that would increase the risk of frailty, except 2 heterogeneous groups of diseases: 'Symptoms, signs & abnormal clinical & laboratory findings, not elsewhere classified' and 'Factors influencing health status & contact with health

services'. The first group comprises diagnoses without a clear identification of the underlying process or pathology. These unspecific signs may be related to undiagnosed chronic conditions such as prostate tumor or heart disease as already underlined by literature<sup>24</sup>. They may also be part of a global "geriatric syndrome"<sup>25</sup>. The diagnoses included in the second group commonly concerned heavy chronic conditions. In both cases, no difference in diagnosis was found between those who maintained a robust status and those who failed.

### **Other factors**

As summarized in a recent systematic review<sup>9</sup>: age, polypharmacy, comorbidity, depression and social situation were also found to be significantly associated with increased risk of incident frailty. Others factors such as gender are inconsistently associated with frailty transitions in the literature. In the present study, gender was not associated with any kind of transition, probably because the analysis took into account depression and polypharmacy, which are 2 major determinants of frailty more often found among women<sup>26,27</sup>. Overweight, obesity, and tobacco consumption were not significantly associated with incident frailty. However, we did not take into account the history of exposure to these factors, long-term effects may be under-evaluated in the present analysis.

### **Strength and limitations**

The main strength of this study lies in its population size and follow-up. The French National Health Data System granted an exhaustive record of hospitalization even though it was not specifically built for epidemiological purposes.

However, several limitations must be acknowledged. First, the causality of events could not be ascertained. We did not know when changes in frailty states occurred nor their exact temporal relationship with hospitalizations. More frequent assessments of frailty, as previously done for disability<sup>28</sup> could help clarifying the temporality of the relationship. However, such a design

would not eliminate indication bias, where the part of frailty attributable to an acute or chronic disease is difficult to disentangle from the part caused by iatrogenic component of hospitalizations. Secondly, comorbidities were self-reported and their severity not assessed, preventing us to use comorbidity indexes requiring clinical examination, or an assessment of the severity of health disorders, or may be restricted by data availability for non-hospitalized individuals for database driven index<sup>29</sup>. Thirdly, hospitalizations characteristics were assessed in separate models due to collinearity issues. As a consequence, cumulative effects and interactions were not evaluated in this study. Finally, hospitalizations were considered as punctual and independent events. No information was available on general practitioner, neither psychiatric ward nor rehabilitation services use. This study did not take into account the diversity of care paths in which hospitalizations fitted<sup>30,31</sup>.

### **Implications and perspectives**

Hospitalization features studied here could easily be collected, directly from hospital reports or patients. Practitioners might gain insights about the near future of their patients after discharge. Hospitalization features can help identifying individuals for whom the follow-up must be reinforced after hospitalization to prevent frailty and, in turn, to prevent physical and functional impairments<sup>32</sup>. Another application could be to identify patients likely to benefit from prehabilitation<sup>33-35</sup>, before planned hospitalizations. However further work is needed to confirm our findings in other settings and to study how they could help improving the management of the hospitalized elderly.

### **Conclusion**

This study showed that some kinds of hospitalizations are associated with incident frailty among robust individuals and impeded recovery among frail individuals. These results highlight the interrelationship between hospitalizations and frailty and should increase

awareness of care providers towards hospitalized people at risk of frailty. Studies combining a wider spectrum of information at the individual (clinical information, care pathways) and contextual level (availability and coordination of health services) are required to improve our understanding and management of frailty.

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**Table 1: Characteristics of the study sample, by year**

		2012	2013	2014
Variables		(n=11891)	(n=12405)	(n=11732)
Sex	Female	3089 (26)	3233 (26)	3051 (26)
Age	less than 65	3847 (32)	2488 (20)	1165 (10)
	65 to 70	5492 (46)	6259 (50)	6125 (52)
	70 and over	2552 (21)	3658 (29)	4442 (38)
Frailty		1664 (14)	1766 (14)	1945 (17)
Hospitalization		1443 (12)	1563 (13)	1537 (13)
Body Mass Index	Low	1614 (14)	1638 (13)	1564 (13)
	Normal	5908 (50)	6010 (48)	5645 (48)
	High	4219 (35)	4344 (35)	4128 (35)
Tobacco	Non - smoker	10476 (88)	1079 (86)	9356 (80)
	Little smoker	537 (5)	546 (4)	485 (4)
	Medium and heavy smoker	359 (3)	333 (3)	290 (2)
Social situation	Disadvantaged	1214 (10)	715 (6)	645 (5)
	Neutral	9094 (76)	9648 (78)	9132 (78)
	Comfortable	1582 (13)	2042 (16)	1955 (17)
Polypharmacy	0 to 4	6958 (59)	7193 (58)	6750 (58)
	5 to 9	3904 (33)	4153 (33)	4019 (34)
	10 or more	1029 (9)	1059 (9)	963 (8)
Comorbidity score	0	1973 (17)	2119 (17)	1827 (16)
	1	4941 (42)	4996 (40)	4672 (40)
	2 and more	4977 (42)	5290 (43)	5233 (45)
Depression		2943 (25)	3096 (25)	3247 (28)

Results expressed as size (percentage) for categorical data and as mean (standardized deviation) for continuous data.

**Table 2: Details of intervening hospitalization characteristics during the study period.**

Variables		First period interval	Second period interval
Number of hospitalized individuals		1453 (12)	1472 (13)
Hospitalizations per individuals	Conti.	1.47 ( $\pm$ 1.76)	1.50 ( $\pm$ 1.71)
	1	1092 (71)	1083 (74)
	2 to 4	334 (23)	356 (24)
	5 & more	27 (2)	33 (2)
Maximal <sup>1</sup> duration (in days)	Conti.	6.19 ( $\pm$ 10.0)	6.66 ( $\pm$ 10.6)
	1	274 (19)	266 (18)
	2 to 3	447 (31)	461 (31)
	4 to 6	294 (20)	312 (21)
	a week or more	438 (30)	433 (30)
Cumulative <sup>1</sup> duration (in days)	Conti.		
	1	8.2 ( $\pm$ 19.0)	8.9 ( $\pm$ 21.2)
	2 to 3	255 (18)	241 (16)
	4 to 6	402 (28)	427 (29)
	A week or more	290 (20)	301 (21)
		506 (35)	503 (34)
Emergencies department use <sup>2</sup>		319 (22)	357 (24)
Surgery classification in DRG <sup>2</sup>		870 (60)	867 (59)
Maximal <sup>1</sup> severity according to CC	1	974 (67)	930 (63)
	2	280 (19)	292 (20)
	3	137 (9.4)	164 (11)
	4	62 (4.3)	86 (5.8)
<b>Major diagnostic category <sup>2</sup> according to ICD-10</b>			
Certain infectious & parasitic diseases	A00-B99	15 (1.0)	18 (1.2)
Cancers	C00-D48	258 (18)	258 (18)

Diseases of the blood & blood-forming organs & certain disorders involving the immune mechanism	D50-D89	11 (0.8)	14 (1.0)
Endocrine, nutritional & metabolic diseases	E00-E90	38 (2.6)	31 (2.1)
Mental & behavioral disorders	F00-F99	19 (1.3)	7 (0.5)
nervous system diseases	G00-G99	42 (2.9)	57 (3.9)
eye & adnexa diseases	H00-H59	44 (3.0)	51 (3.5)
circulatory system diseases	I00-I99	285 (20)	298 (20)
lung diseases	J00-J99	52 (3.6)	50 (3.4)
digestive system diseases	K00-K93	178 (12)	176 (12)
skin & subcutaneous tissues diseases	L00-L99	16 (1.1)	13 (0.9)
musculoskeletal system & connective tissues diseases	M00-M99	237 (16)	247 (17)
genito-urinary system diseases	N00-N99	148 (10)	130 (8.8)
Symptoms, signs & abnormal clinical & laboratory findings, not elsewhere classified	R00-R99	99 (6.8)	92 (6.3)
Injury, poisoning & certain other consequences of external causes	S00-T98	92 (6.3)	99 (6.7)
Factors influencing health status & contact with health services	Z00-Z99	192 (13)	224 (15)

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<sup>1</sup>: maximal value among hospitalizations. <sup>2</sup>: observed at least once during individual follow-up.

Results expressed as size (percentage) for categorical data and as mean (standard deviation) for continuous data.

DRG: diagnostic related group.

CC: comorbidities and complications classes.

ICD-10: 10<sup>th</sup> International Classification of Diseases.

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**Table 3: Factors associated with transitions in frailty status**

Variables		Robust to frail	Frail to robust
Hospitalizations	Yes vs no	1.14 [0.97 – 1.35]	0.89 [0.73 – 1.08]
Sex	Female	1.10 [0.94 - 1.28]	0.87 [0.73 - 1.03]
Age (ref. “less than 65”)	65 - 70	1.03 [0.84-1.26]	0.73 [0.59 - 0.90]
	70 & more	1.29 [1.05 - 1.58]	0.59 [0.48 - 0.74]
Social status (ref. “intermediate”)	disadvantaged	1.00 [0.78 - 1.30]	0.81 [0.62 - 1.07]
	comfortable	0.83 [0.70 - 0.99]	1.09 [0.89 - 1.33]
Live	Alone	0.90 [0.77 -1.06]	0.93 [0.78 - 1.11]
Body Mass Index (ref. “normal”)	underweight	1.13 [0.95 - 1.35]	0.67 [0.55 - 0.83]
	overweight	0.92 [0.81 - 1.05]	0.87 [0.75 - 1.01]
Tobacco (ref. “non smoker”)	little	1.03 [0.77 - 1.37]	1.20 [0.87 - 1.65]
	medium heavy	1.06 [0.76 - 1.47]	0.77 [0.52 - 1.15]
	smoker		
Polypharmacy (ref. “0 to 4”)	5 to 9	1.33 [1.17 - 1.52]	0.88 [0.76 - 1.02]
	10 & more	1.61 [1.32 - 1.96]	0.76 [0.61 - 0.95]
Comorbidity score (ref. “no comorbidity”)	1	1.54 [1.23 - 1.92]	1.02 [0.80 - 1.32]
	2 & more	2.09 [1.67 - 2.61]	0.88 [0.69 - 1.13]
Depression		2.05 [1.81 - 2.32]	0.74 [0.64 - 0.85]

Results expressed as adjusted hazard ratio with 95% confidence interval



**Table 4: Multi-state models results with hospitalizations' characteristics variables.**

Variables		Robust → Frail	Frail → Robust
≥1 hospitalization		1.14 [0.97 - 1.35]	0.89 [0.73 - 1.08]
Number of hospitalizations (+1)		1.03 [0.99 - 1.07]	0.95 [0.86 - 1.05]
Hospitalizations	unique	1.07 [0.88 - 1.30]	0.92 [0.74 - 1.14]
	multiple	1.32 [1.01 - 1.74]	0.78 [0.54 - 1.12]
Length of stay (maximum)	1 to 4 days	1.14 [0.92 - 1.42]	0.80 [0.61 - 1.05]
	4 days or more	1.13 [0.91 - 1.42]	0.97 [0.76 - 1.24]
Length of stay (cumulative)	1 to 4 days	1.15 [0.91 - 1.44]	0.83 [0.63 - 1.10]
	4 days or more	1.13 [0.91 - 1.40]	0.97 [0.73 - 1.19]
Severity	grades 1 or 2	1.08 [0.90 - 1.29]	0.85 [0.69 - 1.05]
	grades 3 or 4	1.50 [1.05 - 2.15]	1.09 [0.71 - 1.68]
Emergency department use	with	1.38 [1.03 - 1.85]	0.93 [0.66 - 1.32]
	without	1.07 [0.88 - 1.29]	0.87 [0.70 - 1.09]
Surgery	with	1.00 [0.81 - 1.23]	0.74 [0.56 - 0.96]
	without	1.36 [1.08 - 1.73]	1.08 [0.84 - 1.40]
Certain infectious & parasitic diseases	with	1.70 [0.48 - 5.95]	1.03 [0.34 - 3.11]
	without	1.13 [0.96 - 1.34]	0.88 [0.73 - 1.08]
Cancers	with	1.12 [0.78 - 1.61]	0.99 [0.62 - 1.57]
	without	1.15 [0.96 - 1.37]	0.87 [0.71 - 1.07]
Diseases of the blood & blood-forming organs & certain disorders involving the immune mechanism	with	2.65 [0.81 - 8.73]	0.46 [0.06 - 3.37]
	without	1.13 [0.96 - 1.34]	0.89 [0.74 - 1.08]
Endocrine, nutritional & metabolic diseases	with	1.65 [0.55 - 5.02]	2.42 [0.95 - 6.20]
	without	1.13 [0.96 - 1.34]	0.86 [0.71 - 1.05]
Mental & behavioral disorders	with	0.99 [0.23 - 4.26]	1.02 [0.29 - 3.56]
	without	1.14 [0.97 - 1.35]	0.88 [0.73 - 1.07]
nervous system diseases	with	1.61 [0.80 - 3.20]	0.77 [0.23 - 2.53]

	without	1.12 [0.95 - 1.33]	0.89 [0.73 - 1.08]
eye & adnexa diseases	with	1.20 [0.55 - 2.62]	0.80 [0.29 - 2.20]
	without	1.14 [0.96 - 1.33]	0.89 [0.73 - 1.08]
circulatory system diseases	with	0.96 [0.68 - 1.35]	0.85 [0.57 - 1.25]
	without	1.19 [1.00 - 1.43]	0.90 [0.73 - 1.11]
respiratory system diseases	with	0.77 [0.30 - 1.94]	1.21 [0.52 - 2.83]
	without	1.15 [0.98 - 1.37]	0.88 [0.72 - 1.07]
digestive system diseases	with	1.27 [0.82 - 1.97]	1.00 [0.61 - 1.63]
	without	1.12 [0.94 - 1.34]	0.87 [0.71 - 1.07]
skin & subcutaneous tissue diseases	with	1.39 [0.41 - 4.70]	0.60 [0.09 - 4.25]
	without	1.14 [0.96 - 1.34]	0.89 [0.73 - 1.08]
musculoskeletal system & connective tissue diseases	with	1.25 [0.89 - 1.75]	0.59 [0.36 - 0.96]
	without	1.12 [0.93 - 1.34]	0.96 [0.78 - 1.17]
genito-urinary system diseases	with	0.93 [0.59 - 1.62]	1.01 [0.61 - 1.69]
	without	1.16 [0.98 - 1.38]	0.87 [0.71 - 1.07]
Symptoms, signs & abnormal clinical & laboratory findings, not elsewhere classified	with	1.70 [1.01 - 2.86]	1.10 [0.61 - 1.97]
	without	1.10 [0.93 - 1.31]	0.87 [0.71 - 1.07]
Injury, poisoning & certain other consequences of external causes	with	1.06 [0.60 - 1.87]	0.60 [0.28 - 1.29]
	without	1.15 [0.97 - 1.36]	0.91 [0.75 - 1.11]
Factors influencing health status & contact with health services	with	1.51 [1.06 - 2.14]	0.79 [0.49 - 1.29]
	without	1.08 [0.90 - 1.29]	0.90 [0.74 - 1.11]

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All models were run separately, Results expressed as adjusted hazard ratio with 95% confidence interval.

Adjustment : age, sex, marital status, social status, BMI, comorbidity score, tobacco consumption, polypharmacy, self-reported depression

reference group: "no hospitalization"