Functional decline in geriatric rehabilitation ward; is it ascribable to Hospital Acquired Infection? A prospective cohort study.

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Abstract

Background: Some patients may not benefit from their stay in a geriatric rehabilitation unit and paradoxically worsened their functional status. The incidence of functional decline in these units and factors associated with this decline have not been clearly identified.

Methods: We used a prospective cohort of consecutive patients aged ≥ 75 years admitted to a geriatric rehabilitation unit in a French university hospital. The main endpoint was functional decline defined by at least an one-point decrease in Activities of Daily Living (ADL) score during the stay. Baseline social and geriatric characteristics were recorded and comorbidities were sought by the Cumulative Illness Rating Scale for Geriatrics (CIRS-G). During follow-up, hospital-acquired infection (HAI) was recorded, as was ADL score at discharge. Multivariate logistic regression and mediation analyses were used to identify factors associated with ADL decrease.

Results : Among the 252 eligible patients, 165 (median age 85 years [interquartile range (IQR) 81-90] had available ADL scores at baseline (median score 7 [IQR 4-10]) and at discharge (median 9 [6-12]). Median CIRS-G score was 11 [9-13], 24 (14.5%) had a pulmonary HAI; 30 (18.2%) showed functional decline. On multivariable analysis, functional decline was associated with comorbidities (global CIRS-G score, P=0.02, CIRS-G for respiratory disease [CIRS-G-R] ≥2, P=0.03, or psychiatric disease, P=0.02) and albumin level < 35 g/l (p=0.02). Significant association were found between functional decline and CIRS-G for respiratory diseases (CIRS-G-R) (OR 2.82 [95% CI 1.18-6.71], p=0.016), between functional decline and pulmonary HAI (OR 4.09 [1.48-11.34],p=4.09), and between CIRS-G-R and pulmonary HAI (OR 10.9 [5.26-22.5],p=0.0001). Theses associations and the reduced effect of CIRS-G-R on functional decline after adjusting for pulmonary HAI (OR 1.91 [0.71-5.16], p=0.20) suggested partial mediation of pulmonary HAI in the relation between CIRS-G-R and functional decline.

Conclusion : Baseline comorbidities were independently associated with functional decline in patients hospitalized in a geriatric rehabilitation unit. Pulmonary HAI may have mediated this association. We need to better identify patients at risk of functional decline before transfer to a rehabilitation unit and to test the implementation of modern and individual programs of rehabilitation outside the hospital for these patients.

Background

Hospital admissions are important causes of functional decline among older patients (1). The decline has important effects on quality of life and is associated with increased risk of longer hospital stay, death, nursing home transfer, and rehospitalization (2–4). Older age, preexisting altered functional status, cognitive impairment, low mobility during the stay and length of stay have been reported to increase the risk of functional decline in acute unit (5–12).

In some European countries, including France, older patients with functional decline in acute units are transferred to geriatric rehabilitation units (1, 13–15) that are inpatient units specialized in the

multidisciplinary rehabilitation of older frail patients with chronic diseases and geriatric syndromes (16). A meta-analysis showed that these units may improve functional status and may limit nursing-home transfer and mortality (17). One study suggested that some patients may not benefit from their stay in a geriatric rehabilitation unit and paradoxically worsened their functional status (18). The incidence of functional decline in these geriatric rehabilitation units and factors associated with this decline have not been clearly identified (16). Previous studies in rehabilitation units focused on specific groups of patients, such as those with hip fracture (18–23) or cognitive impairment (7, 18), which implies a difficult transfer to real-life rehabilitation units. As compared with younger patients, older patients admitted to a geriatric rehabilitation unit had multiple comorbidities in addition to the primary diagnosis that triggered their admission to the rehabilitation unit (22, 24).

Results concerning comorbidities as predictors of functional outcome for older frail patients are discordant (5, 21–29). Mechanisms that could tie baseline comorbidities to rehabilitation performance remain unclear (21, 22, 24–28). Moreover, previous prognostic models are based on only baseline parameters. Some acute factors occurring during hospitalization such as hospital-acquired infection (HAI) could affect the relation between comorbidities and functional decline. The prevalence of HAI was higher in rehabilitation. HAIs remain a major cause of morbidity and mortality despite advances in antimicrobial therapy, better supportive care modalities, and the use of a wide range of preventive measures (30).

The aim of this study was to assess the frequency of functional decline in older patients during a stay in a rehabilitation unit and factors associated with this functional decline, with a specific focus on the role of HAI.

Methods

Study design and patients

We used data from a previously described prospective cohort study conducted between July 2006 and November 2008 in a teaching hospital (1300 beds) in the Paris area, France (31). The cohort comprised 252 consecutive patients aged 75 years or older who were referred to a geriatric rehabilitation unit from acute medical or surgical units during the study period.

In addition to medical care provided by geriatricians and standard nursing care, inpatient rehabilitation typically included both physical therapy (1 hr/day) and occupational therapy (1 hr/day) on 5 of 7 days per week. Inclusion criteria were medically stable status at admission, need for long-term care and rehabilitation, and absence of terminal disease (e.g., uncontrolled malignancy or severe dementia), fever, infection, cancer, or known immunological dysfunction. All patients underwent routine assessment by multi-disciplinary staff including physicians, nurses, a physical therapist, and a social worker. Patients were followed up until death, discharge from the rehabilitation unit or up to 3 months after inclusion. The study complied with the Declaration of Helsinki and was approved by the Paris XII ethics committee (no.

SCR06010), Paris, France. Written informed consent was obtained from each patient before study inclusion.

Data collection

Baseline data were collected for each patient, using a standardized form before admission to the geriatric rehabilitation unit. Comorbidities were evaluated using the Cumulative Illness Rating Scale for Geriatrics (CIRS-G) (32), which scores diseases in 14 organ systems on a 0–4 grading scale of severity (a higher score indicates higher comorbidity). The comorbidity index (CIRS-G Index) was calculated as the number of domains with score ≥ 2 and ranged from 0 to 14. The 14 domains were also assessed separately and were considered altered with CIRS-G score ≥ 2. Cognitive function was assessed by the Mini-Mental State Examination (MMSE, score < 24 considered abnormal) (33) and renal function by the Cockroft creatinine clearance (ml/min) (34). Serum albumin level < 35 g/L was considered low (35). Functional status was assessed by trained rehabilitation unit staff by the ADL scale, with scores ranging from 0 to 12, 12 indicating no impairment in all 6 activities, (bathing, dressing, toilet use, continence, transfer and feeding). For each activity, the score could be 0 (unable to perform the activity without complete help), 1 (able to perform the activity with little assistance), and 2 (able to perform the activity without any help) (36). ADL was also assessed at discharge from the rehabilitation unit.

During follow-up, 2 of the co-authors (ML and EL) visited each patient and reviewed the medical records with the attending physician and nurses to assess HAI in the rehabilitation unit. HAI was defined as a well-documented infection that was not present nor starting at admission and that met the Centers for Disease Control and Prevention definition of nosocomial infection (37).

Outcome

The outcome was functional decline defined by at least a one-point decrease in ADL score during the rehabilitation unit stay.

Statistical analysis

Categorical variables are described as numbers (%) and were compared by chi-square test or Fisher exact test, as appropriate. Quantitative variables are described as median (interquartile range [IQR]) and were compared by the nonparametric Mann-Whitney test. Characteristics of patients with unavailable ADL data at discharge were compared to those with available data. Considering this latter group, we then compared the groups with and without functional decline in terms of baseline characteristics. Logistic regression modeling was used to estimate odds ratios (ORs) with their 95% confidence intervals (95% CIs). Variables associated with functional decline on univariate analysis at $P < 0.15$ were then entered into a multivariate logistic regression model. To avoid introducing strongly correlated variables into multivariate models, we assessed correlations by using Cramer's V for categorical variables and the nonparametric Spearman's rank correlation coefficient (Rho) for quantitative variables. All models including albumin level were systematically adjusted for C-reactive protein (CRP) level, as appropriate (35). Finally, and in accordance with our hypothesis, we examined whether HAI occurrence potentially

mediated the relation between comorbidities and functional decline, as illustrated in the conceptual framework shown in Fig. 1. According to Baron and Kenny (38), evidence for a partial mediating effect was assessed by the statistical significance (38–41) of the following associations:
1) between comorbidities as the independent exposure of the interest (A) and functional decline as the outcome (Y),
2) between comorbidities and HAI as the mediating factor (M),
3) and between HAI and functional decline
and by a reduced effect of comorbidities on functional decline after adjusting for HAI.

Sensitivity analyses

To test the robustness of our results, we performed three sensitivity analyses on the final models. Using the hypothesis of maximal bias, we first considered that all patients with missing discharged ADL data had functional decline, and second that these patients had no functional decline. Finally, we used a multiple imputation approach with the multiple-multivariate imputation-by-chained-equations procedure with the missing-at-random assumption. We used all baseline covariates and outcomes together to impute missing data values and independently analyzed 20 copies of the data.

All tests were two-tailed. $P \leq 0.05$ was considered statistically significant. Data were analyzed by using STATA v11.0 (StataCorp, College Station, TX, USA).

Results

The 15 patients who died during their stay in the rehabilitation unit were not included in the present study. Among the remaining 237 patients, 72 (30.3%) had missing ADL data at discharge. These patients were older, had lower admission ADL values, a higher number of comorbidities and a higher rate of HAI during rehabilitation stay than the 165 patients with available data (all $p < 0.05$) (supplemental data – Appendix 1).

Among the 165 patients with available ADL data at discharge, 30 (18.2%) showed functional decline during the rehabilitation stay and 51 (30.9%) had a HAI (Table 1). Median ADL at discharge from the rehabilitation unit was significantly lower for patients with than without functional decline (4 [1–9] vs 10 [6–12], $P < 0.0001$). Median length of unit stay was 29 days [15–63], with no difference between the groups with and without functional decline (median 32 days [13–71] vs 29 days [15–60], $P = 1$). On univariate analysis, global CIRS-G and CIRS-G Index were significantly higher for patients with than without functional decline. Among the CIRS-G categories, respiratory and psychiatric diseases were significantly more prevalent in patients with functional decline. These patients had also lower MMSE values and low albumin level. The occurrence of pulmonary HAI was significantly associated with functional decline but also with CIRS-G ≥ 2 for respiratory diseases (OR 10.9 [5.26–22.5], $P < 0.0001$). Functional decline was associated but not significantly with admission ADL value, CIRG-G ≥ 2 for genitourinary domain and CRP level.

Table 1

Characteristics of older patients with or without functional decline during a rehabilitation unit stay and associated factors.

		Functional decline* during rehabilitation unit stay			
	Study population n = 165 (%)	Yes n = 30 (%)	No n = 135 (%)	Crude OR [95% CI] †	P value ‡
Baseline characteristics					
Age, years, median [Q1-Q3]	84 [80–88]	83 [81–88]	84 [80–88]		0.80
Male sex	44 (26.7)	9 (30)	35 (25.9)		0.65
Living alone	113 (68.5)	20 (66.7)	93 (68.9)		0.81
Place of residence:					
Home or assisted-living facility	159 (96.4)	29 (96.7)	130 (96.3)		0.92
Nursing home	6 (3.6)	1(3.3)	5 (3.7)		
Main acute diagnosis					0.35
Cardiovascular diseases	36 (21.8)	6 (20)	30 (22.2)		
Cerebrovascular diseases	55 (33.3)	14 (46.7)	41 (30.4)		
Orthopedic diseases (including fracture)	35 (21.2)	4 (13.3)	31 (23)		
Other diagnosis§	39 (23.6)	6 (20)	33 (24.4)		
ADL at admission in rehabilitation unit, median [Q1-Q3]	7 [4–10]	5 [2–10]	7 [4–10]	0.9 [0.8–1.01]	0.07
Comorbidities					
Global CIRS-G, median [Q1-Q3], $OR/_{1-point\ increase}$ (n = 164)	11 [9–13]	12.5[10–16]	10.5 [8–13]	1.16 [1.04–1.28]	0.001

		Functional decline* during rehabilitation unit stay			
CIRS-G Index, median [Q1-Q3], OR/$_{1\text{-point increase}}$	5 [4–6]	6 [4–7]	4 [3–5]	1.46 [1.15–1.84]	0.0002
Number of patients with CIRS-G score ≧ 2 in each category, n (%)					
Cardiovascular/respiratory system					
1. Heart disease	106 (64.2)	22 (73.3)	84 (62.2)		0.25
2. Hypertension	120 (72.7)	20 (66.7)	100 (74.1)		0.41
3. Vascular/hematological diseases	45 (27.3)	9 (30)	36 (26.7)		0.71
4. Respiratory diseases	34 (20.6)	11 (36.7)	23 (17)	2.82 [1.18–6.71]	0.016
5. Eye, ear, nose and larynx diseases	36 (21.8)	6 (20)	30 (22.2)		0.79
Gastrointestinal system					
6. Upper gastrointestinal diseases	13 (7.9)	3 (10)	10 (7.4)		0.63
7. Lower gastrointestinal diseases	15 (9.1)	4 (13.3)	11 (8.1)		0.37
8. Hepatic diseases	1 (0.6)	0 (0)	1 (0.7)		0.63
Genitourinary system					
9. Renal diseases	60 (36.4)	15 (50)	45 (33.3)	2 [0.90–4.45]	0.09
10. Other urogenital diseases	35 (21.2)	10 (33.3)	25 (18.5)	2.2 [0.92–5.27]	0.07
Musculoskeletal/intergumentary system					
11. Muscle, bone, and skin diseases	85 (51.5)	18 (60)	67 (49.6)		0.30
Neuropsychiatric system					
12. Neurological diseases	47 (28.5)	12 (40)	35 (25.9)	1.90 [0.83–4.35]	0.12

		Functional decline* during rehabilitation unit stay			
13. Psychiatric diseases	125 (75.8)	27 (90)	98 (72.6)	3.40 [0.97–11.87]	0.04
General system					
14. Endocrine and metabolic diseases	46 (27.9)	11 (36.7)	35 (25.9)		0.23
MMSE, median [Q1-Q3], OR/$_{1-point\ decrease}$	22 [17–26]	18 [15–25]	22.5 [18–26]	1.08 [1.01–1.17]	0.031
MMSE < 24	91 (57.2)	20 (69)	71 (54.6)		0.16
Albumin level < 35 g/L	31 (18.8)	11 (36.7)	20 (14.8)	3.24 [1.30–8.04]	0.006
CRP level, mg/L, median [Q1-Q3]	6 [2.5–18]	8 [2.5–19]	5 [2.5–13]	1.01 [0.99–1.04]	0.10
Creatinine clearance Cockroft, ml/min, median [Q1-Q3], OR/$_{1-point\ decrease}$ (n = 164)	42[32.7–54.6]	50.8 [31.4–55.6]	40.5 [32.7–53.3]		0.26
Hospital-acquired infection					
Acquired infection during rehabilitation period ‖	51 (30.9)	13 (43.3)	38 (28.1)	1.95 [0.87–4.40]	0.104
Acquired pulmonary infection	19 (11.5)	9 (30)	15 (11.1)	4.09 [1.48–11.34]	0.008
Acquired urinary infection	25 (15.1)	5 (16.7)	20 (14.8)		0.80
Other acquired infections	5 (3.0)	0 (0)	5 (3.7)		0.29

Abbreviation: OR, odds ratio; CI, confidence interval; ADL, activities of daily living; CIRS-G, Cumulative Illness Rating Scale for Geriatrics; CRP, C–reactive protein; MMSE, Mini-Mental State Examination

The CIRS-G consists of 14 domains related to different body systems. Scoring on the different domains is weighted by the severity of the comorbid condition. Severity scores range from 0 (none) to 4 (extremely severe). The global score is the sum of each of the 14 domain scores. The CIRS-G index was calculated as the number of categories with score ≥ 2.

(n=) indicates the number of patients with available data.

	Functional decline* during rehabilitation unit stay
* Functional decline was defined by at least a one-point decrease in ADL score during the rehabilitation unit stay.	
† Unadjusted ORs are provided for variables associated with functional decline at P < 0.15.	
‡ P value by chi-square, Fisher exact, or Kruskal Wallis test as appropriate.	
§Including respiratory, gastrointestinal, and osteoarticular disease other than fracture.	
‖Some patients had two or more acquired infections, so the sum of the patients in the three acquired infection groups is > 51.	

Because of co-linearity between overall (CIRS-G Index) and specific measures of severe comorbidities (CIRS-G ≥ 2 for respiratory or psychiatric diseases), we created two separate models, with the CIRS-G Index or with specific CIRS-G domains. MMSE, strongly associated with CIRS-G ≥ 2 for psychiatric diseases (rho 0.41, p < 0.0001), was not introduced in the model with specific domains.

Table 2 shows factors independently associated with functional decline during the rehabilitation unit stay. On multivariate analysis, functional decline was significantly associated with the CIRS-G Index, with a non-significant association for low albumin level and low MMSE values (Table 2, model 1). Two CIRS-G–specific domains, namely respiratory and psychiatric diseases, and low albumin level were independently associated with functional decline (Table 2, model 2). Systematic adjustment on admission ADL value did not change the results (data not shown). After adjustment for CIRC-G index or CIRS-G for respiratory or psychiatric diseases, functional decline was not significantly associated with admission ADL value, pulmonary HAI, or CIRS-G ≥ 2 for renal or other urogenital diseases.

Table 2
Factors independently associated with deteriorated activities of daily living (ADL) during the rehabilitation unit stay.

	Model 1 Adjusted OR [95%CI]	P value	Model 2 Adjusted OR [95%CI]	P value
CIRS-G Index	1.34 [1.04–1.74]	0.02		
CIRS-G score ≥ 2 for respiratory diseases			2.89 [1.12–7.53]	0.03
CIRS-G score ≥ 2 for psychiatric diseases			4.82 [1.27–18.25]	0.02
Albumin level < 35 g/l	2.49 [0.95–6.57]	0.06	3.05 [1.17–7.96]	0.02
$MMSE_{1\text{ – point decrease}}$	1.07 [0.99–1.16]	0.09		
Adjusted ORs were estimated by logistic regression adjusted for all variables in the table, with routine adjustment for CRP level (P value: Wald test).				
MMSE Mini-Mental State Examination; CIRS-G Cumulative Illness Rating Scale for Geriatrics, CIRS-G Index calculated as the number of categories with score ≥ 2. Model 1 considers factors associated with ADL deterioration and is adjusted by CIRS-G index, albumin level < 35 g/l, and MMSE. Model 2 considers factors associated with ADL deterioration and is adjusted for CIRS-G score ≥ 2 for respiratory and psychiatric diseases and albumin level < 35 g/l.				

Significant or trend associations were observed 1/ between CIRS-G ≥ 2 for respiratory diseases and functional decline (crude OR 2.82 [95% CI 1.18–6.71]), 2/ between CIRS-G ≥ 2 for respiratory diseases and pulmonary HAI (crude OR 10.9 [5.26–22.5], p < 0.0001), and 3) between pulmonary HAI and functional decline (OR 4.09 [1.48–11.34]). The reduced effect of CIRS-G ≥ 2 for respiratory diseases on functional decline observed after adjusting for pulmonary HAI (OR 1.91 [0.71–5.16], p = 0.20) (Table 2) suggested partial potential mediation of acquired pulmonary HAI in the relation between CIRSG ≥ 2 for respiratory diseases and functional decline.

Sensitivity analyses

The three sensivity analyses produced similar results (supplemental data – Appendix 2)

Discussion

Among patients 75 years and older referred to a geriatric rehabilitation unit from acute medical or surgical units, 18% had functional decline during their hospitalization in the rehabilitation unit. Factors independently associated with functional decline were comorbidities assessed by the CIRS-G index and specifically the CIRS-G ≥ 2 for respiratory or psychiatric diseases. Our results also suggest that

pulmonary HAI in patients hospitalized in rehabilitation units may mediate the relation between CIRS-G ≥ 2 for respiratory diseases and functional decline.

To our knowledge, no previous study has estimated the frequency of acquired functional decline, assessed by ADL, in older patients during a rehabilitation unit stay. In previous studies, functional improvement was assessed with different tools such as the Functional Independence Measure (18, 19, 21, 22, 25, 29) or the Barthel Index (23). Comparing studies is difficult because of the heterogeneity of these tools. In keeping with two previous studies (29, 42), advanced age was not associated with functional decline.

In our study, comorbidities assessed by the CIRS-G, particularly severe psychiatric and respiratory diseases, were significant predictors of functional decline during the rehabilitation stay. One meta-analysis (22) showed that results concerning the association between functional decline and comorbidities are discordant. Tools used to assess comorbidities are heterogeneous. The main tools used are the Charlson comorbidity index, the comorbidity Index of Liu, the Comorbidity Severity Index or the CIRS-G. Only studies assessing comorbidities with indexes taking into account the severity of diseases such as the CIRS-G and not simple counts of comorbidities found an association between comorbidities and functional status (21, 24–27).

Our findings are consistent with previous studies showing that cognitive impairment and depressive symptomatology predicted poor rehabilitation (7, 43, 44). Similarly, in one cohort of 459 older patients hospitalized in a general medical service, risk of 1-month functional decline was two- to three-fold higher for patients with depression, delirium or with the overlap syndrome of depression and delirium than patients with neither depression nor delirium (45)

The CIRS-G ≥ 2 for respiratory diseases was associated with functional decline and with pulmonary HAI. Reduction of exercise due to respiratory diseases may lead to peripheral muscle dysfunction and therefore functional decline.(46). An association between chronic respiratory diseases and pulmonary HAI was previously described in one Spanish study of a subacute care unit with frail older patients (28). Inflammatory cytokine levels (tumor necrosis factor α) are increased with pulmonary infection and could lead to functional decline(47).

We found an association, between low albumin level at admission, as assessed by serum albumin level, and functional decline persisting after adjustment for an inflammation marker (CRP level). Protein-calorie malnutrition, frequent in older people, leads to muscular loss and may explain this association.(48).

Our study has certain strengths. Comorbidities were measured for all participants at baseline and were assessed by using a formal, validated and standard scale of comorbidity taking into account the severity of chronic diseases. This is the first study to analyze the association between functional decline and specific domains of the CIRS-G. This may be the first approach to explain the relation between functional decline and comorbidities, taking into account HAI.

However, the study contains several limitations. First, the single-center design of our study may have led to recruitment bias, thereby limiting external validity. Detailed operational characteristics, such as the intensity and frequency of physical therapy, were not available for each patient (17). Factors other than HAI occurring during the hospital stay could be involved in functional decline. We did not analyze the impact of functional decline on future hospital re-admission, quality of life, and social costs. Finally, from the initial cohort of 252 consecutive patients, only data for 165 were analyzed, which may have led to selection bias. However similar results obtained by sensitivity analyses support the robustness of our findings.

Implications

We need to better identify patients at risk of functional decline before transfer to a rehabilitation unit. It would be interesting to test in France the implementation of modern and individual programs of rehabilitation outside the hospital, such as those from Norway,Suede and Spain (49–51).

Conclusion

The goals of the rehabilitation unit for older patients are to achieve significant functional improvement mainly in mobility, thereby enabling these patients to return home in a relatively short time. However, we found that these tasks can be difficult to achieve in older patients with severe respiratory or psychiatric comorbidities. Pulmonary HAI in patients hospitalized in rehabilitation units may mediate the relation between respiratory diseases comorbidities and functional decline. We need to test the implementation of modern and individual programs of rehabilitation outside the hospital for these frail patients.

Abbreviations

Activities of Daily Living :ADL

Cumulative Illness Rating Scale for Geriatrics :CIRS-G

C-reactive protein CRP

Evelyne Liuu EL

Hospital-Acquired Infection : HAI

Marie Laurent ML

Mini-Mental State Examination : MMSE

InterQuartile Range [IQR]

Odds Ratios ORs

Declarations

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by an institutional review board (local Comitee Paris XII France) in compliance with the French legislation on observational studies (french law 2004 800 6 aout 2004 bioéthique). Number SCR 06 010 was attributed to this study. No ethical problem was found at the end of the evaluation by institutional review board. The study complied with the Declaration of Helsinki. All the study participants received written information about the use of their personal medical data for the study, and provided verbal consent. In compliance with the French legislation on observational studies, written informed consent was not required.

CONSENT FOR PUBLICATION

Written informed consent was obtained from each patient before study inclusion. Written permission has been obtained from all persons named in the Acknowledgments .All nine authors have read and approved the manuscript, and none of the authors has any conflict of interest to report.

COMPETING INTERESTS

The authors declare no conflict of interest.

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AUTHORS' CONTRIBUTIONS

ML, NO,JPD, FCP, LC,EL,EA,SBG and EP made substantial contributions to the conception of the work. ML, EP and SBG also made contributions to design of the work; the acquisition, the analysis and interpretation of data and have drafted the work. NO analyzed and interpreted the patient data and have drafted the work. FCP and EA analyzed and interpreted the patient data. EL and LC interpreted data and had substantively revised the article. ML and EL included patients. ML, NO, EP and SBJ were major contributors in writing the manuscript. All authors read and approved the final manuscript.

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AVAILABILITY OF DATA AND MATERIALS

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.All data generated or analysed during this study are included in this published article [and its supplementary information files].

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Figures

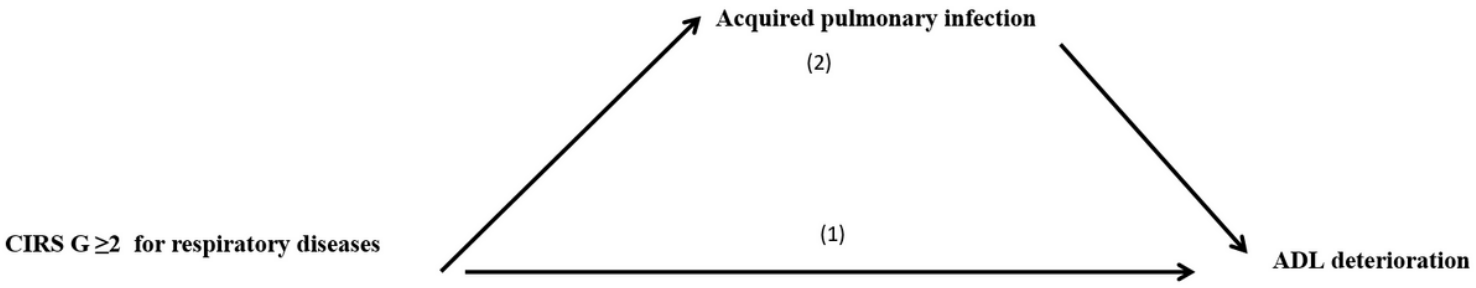

Figure 1

Conceptual framework of the causal structure modelizing mediation. (1) Direct effect of CIRS-G ≥ 2 for respiratory diseases (CIRS-G-R) on activities of daily living (ADL); and (2) indirect effect via acquired pulmonary infection. Legends (A) exposure of interest, (M) mediating factor, (Y) outcome

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