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ORIGINAL RESEARCH

Pain and Frailty in Hospitalized Older Adults

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ABSTRACT

Introduction: Pain and frailty are prevalent conditions in the older population. Many chronic diseases are likely involved in their origin, and both have a negative impact on quality of life. However, few studies have analysed their association.
Methods: In light of this knowledge gap, 3577 acutely hospitalized patients 65 years or older enrolled in the REPOSI register, an Italian network of internal medicine and geriatric hospital wards, were assessed to calculate the frailty index (FI). The impact of pain and some of its characteristics on the degree of frailty was evaluated using an ordinal logistic regression model after adjusting for age and gender.
Results: The prevalence of pain was 24.7%, and among patients with pain, 42.9% was regarded as chronic pain. Chronic pain was associated with severe frailty (OR = 1.69, 95% CI 1.38–2.07). Somatic pain (OR = 1.59, 95% CI 1.23–2.07) and widespread pain (OR = 1.60, 95% CI 0.93–2.78) were associated with frailty. Osteoarthritis was the most common cause of chronic pain, diagnosed in 157 patients (33.5%). Polymyalgia, rheumatoid arthritis and other musculoskeletal diseases causing chronic pain were associated with a lower degree of frailty than osteoarthritis (OR = 0.49, 95%CI 0.28–0.85).
Conclusions: Chronic and somatic pain negatively affect the degree of frailty. The duration and type of pain, as well as the underlying diseases associated with chronic pain, should be evaluated to improve the hospital management of frail older people.

Keywords: Chronic pain; Internal medicine and geriatric wards; Musculoskeletal diseases

Ilaria Ardoino and Carlotta Franchi contributed equally to this work.

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Key Summary Points

Why carry out this study?

Frailty and pain are conditions in which prevalence increases with age.

Many chronic diseases, especially those related to the musculoskeletal system and connective tissue, are involved in the origin of both frailty and pain.

This paper investigates the relation between pain and frailty in hospitalized older patients.

What was learned from the study?

Chronic, widespread and somatic pain were negatively associated with frailty.

The accurate assessment of pain and its therapeutic treatment should be evaluated to improve the management of frail hospitalized older people.

DIGITAL FEATURES

This article is published with digital features to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.12982520.

INTRODUCTION

Age is frequently associated with pain and frailty. Chronic pain is clinically common, being present in about 66% of persons over the age of 65 years and mainly in women, who are affected three times as frequently as men [1–3]. Pain often presents as a recurrent symptom associated with acute and chronic inflammatory processes such as rheumatic and degenerative diseases. Among these, low back pain is the most common, affecting 33% of older people. Osteoarthritis involves major joints in about 12% of the world population, and rheumatoid arthritis is diagnosed in about 1–2% [4]. Pain is also a common symptom accompanying different chronic diseases such as cancer, diabetes, neurodegenerative diseases, and liver, renal and cardiovascular diseases, their common denominators being the presence of chronic pain and advanced age.

Chronic pain impairs quality of life and the ability to maintain an independent lifestyle, productivity and social relationships [5, 6]; thus older people often experience mood and anxiety disorders [7, 8]. Zis and collaborators showed that about 13% of older adults suffered from both major depression and chronic pain simultaneously, although this prevalence may vary in different populations, and the authors highlight how the two conditions might be risk factors for each other [9]. In turn, depression increases the perception of pain, thus triggering a vicious circle, suggesting a possible role of neuroinflammation as a common pathogenic factor for the development of both chronic pain and depression [9]. Apart from depression, many other causes and consequences of chronic pain share common mechanisms with the development of frailty [10].

Frailty is an age-related syndrome due to a multidimensional process leading to increased vulnerability, reduced ability to respond to stressors, adverse health outcomes and also death [12–15]. In older adults, persistent pain might lead to a loss of physiological reserves and impaired mobility, thus contributing to the likelihood of frailty [11]. There is still ongoing debate regarding the most suitable operational definition and assessment instruments for use in clinical practice to define frailty. The frailty phenotype described by Fried, which is based on five criteria related to compromised physical performance [12], and the frailty index (FI) based on age-related accumulation of deficits proposed by Rockwood and Mitnitski are the most common [16]. Regardless of the method, frailty and pre-frailty increase in prevalence with aging and are more frequent in women [12, 17]. These features have similarities with those of chronic pain, such that many causes and effects of pain are embedded in the definition of frailty. There are at the moment only a few studies that directly correlate pain with

frailty [10, 18, 19], and they are confined to the primary care setting. With the hypothesis that early recognition and adequate management of pain might be of crucial importance in hospitalized older adults in order to prevent or slow frailty, the objective of this study was to evaluate whether there was an association between pain and frailty in a population of older patients acutely hospitalized in internal medicine and geriatric wards.

METHODS

Data Collection

Data were obtained from REPOSI (REgistry POlitherapy SIMI), an ongoing collaboration between the Italian Society of Internal Medicine (SIMI), IRCCS Fondazione Ca' Granda Ospedale Maggiore Policlinico and IRCCS "Mario Negri" Institute of Pharmacological Research involving a network of more than 100 internal medicine and geriatric hospital wards throughout Italy. The REPOSI register enrols patients $\geq$ 65 years old acutely admitted to the participating wards during four index weeks 3 months apart. Data were initially obtained every 2 years (in 2010, 2012 and 2014), and are now collected yearly, beginning in 2016. Greater detail is provided elsewhere [15, 20]. The minimum data set includes sociodemographic factors, laboratory parameters, performance in activities of daily living (ADL) according to the Barthel Index (BI) [21], cognitive skills via the Short Blessed Test (SBT) [22], patterns of co-morbidities and their severity according to the Cumulative Illness Rating Scale (CIRS) [23], and drugs prescribed on admission, during hospital stay and at discharge. The study was conducted according to Good Clinical Practice guidelines and the Declaration of Helsinki. The study was approved by the Ethical Committee of the IRCCS Ca' Granda Maggiore Policlinico Hospital Foundation of Milan and by the ethics committees of the participating centres (Supplementary Material). All patients provided signed informed consent.

Pain and Frailty Assessment

Patients enrolled from 2012 onward were eligible for the present analysis, because in previous REPOSI runs, no information on pain was collected. Patients with all the information available for the computation of the frailty index were assessable for the present analysis.

Frailty was measured according to the frailty index previously published within the framework of the REPOSI register [24], and based upon the procedure outlined by Searle [25]. The index includes 34 items related to nutrition using the body mass index (BMI), ability to perform activities of daily living (BI), cognition (SBT), mood (e.g. diagnosis of depression and anxiety), laboratory parameters (e.g. haemoglobin, platelets, white blood cells, creatinine clearance) and main chronic diseases reported in the CIRS (e.g. severity of hypertension, heart failure, ischaemic heart disease, stroke, diabetes, dyslipidaemias, thyroiditis, chronic obstructive pulmonary disease [COPD], kidney failure [CKD], upper and lower gastrointestinal diseases, liver disease, tumours, musculoskeletal diseases, Parkinson disease and psychiatric disorders). Patients were stratified into three groups according to their increasing degree of frailty: not frail (F0), moderately frail (F1) and severely frail (F2). The cut-off values were assessed according the 33th and 67th percentiles of the FI distribution.

Pain and some of its characteristics, including its temporal duration (acute or chronic), type (somatic, visceral, neuropathic), localizations (localized, widespread), causes and intensity (ranked from 0 to 10 according to the Numeric Rating Scale, NRS), were self-reported by patients and assessed at the moment of hospital admission.

Statistical Analysis

Data were summarized as frequencies (%), medians and interquartile ranges (IQR), or means and standard deviations (SD) as appropriate. A proportional odds ordinal logistic regression model (POM) was used to assess whether pain and its characteristics were

associated with increasing severity of frailty. In the ordinal regression model, the response variable was the severity of frailty assessed by the three tiers of the FI introduced above, and all models were adjusted for sex and age.

In the ordinal regression model, the frequencies of each response category (e.g. F2), and of those above (F1/F2), were in turn considered and compared with the frequencies of those below (F1/F0 or F0), so that two separate comparisons were obtained. POM assumes that the effect of any covariate is the same across all comparisons, so that only one set of regression coefficients (and therefore only one odds ratio for each predictor) should be estimated. Accordingly, the regression model can be expressed as:

$$\log\left(\frac{P(Y \geq j|x)}{P(Y < j|x)}\right) = \alpha_j + x'\beta.$$

The POM assumption was checked by the score test and graphical methods. Results were expressed as odds ratio (OR) and 95% confidence interval (CI). The analysis was performed using SAS version 9.4 software (SAS Institute Inc., Cary, NC, USA).

RESULTS

Among 4827 patients enrolled in the REPOSI register since 2012, 3577 (74.1%) were assessable for the computation of the FI. The sample was well balanced for gender, with a mean age (SD) of 79.1 (7.6) years, and the FI distribution was positively skewed, with a mean of 0.27 and SD of 0.14. In particular, 1177 were not frail (F0), with a FI $\leq$ 0.19, 935 were moderately frail (F1), with a FI between 0.19 and 0.32, and 1169 were severely frail (F2), with FI $>$ 0.32. Frailty increased with age, but with no significant difference between males and females after adjustment for age.

Table 1 shows the characteristics of 3577 patients according to the degree of frailty. Among patients, 884 (24.7%) suffered from pain, and in particular 379 (42.9%) had chronic pain. Somatic pain was the most common type of pain occurring in 400 patients (45.2%). Furthermore, 48 patients (5.5%) experienced widespread pain, and among the others, 195 patients (22.3%) suffered from pain involving two or more body sites, mainly the trunk and lower limbs.

Table 2 shows the results from the ordinal logistic regression model. In all the regression models, the chi-square score test failed to reject the null hypothesis of equal regression coefficients across response categories ($p > 0.25$); thus we may conclude that the proportional odds assumption holds. After adjusting for sex and age, there was an overall statistically significant association between pain and frailty (OR = 1.33, 95% CI 1.16–1.54). Specifically only patients suffering from chronic pain, but not those with acute pain, were more likely to be moderately to severely frail than those with no pain (OR = 1.69, 95% CI 1.38–2.07).

Somatic pain was associated with a higher degree of frailty than all other types of pain (OR = 1.60, 95% CI 1.22–2.07). Patients with widespread pain tended to be frailer than those suffering from localized pain (OR = 1.60, 95% CI 0.93–2.78), regardless of the number or specific sites involved. No relation was found between pain intensity and frailty, either in the overall population or in those with chronic pain.

Musculoskeletal conditions were the most common cause of persistent pain, particularly osteoarthritis, which accounted in our sample for almost one third of the cases, followed by rheumatoid arthritis and other rheumatic conditions (18.0%). Cancer was the other most frequent condition (Table 3). No relevant difference was found among the diseases leading to chronic pain (Table 4), but a lower degree of frailty was found in patients with pain caused by rheumatic conditions (OR = 0.49, 95%CI 0.28–0.85).

DISCUSSION

This study investigated the association between pain and frailty along with its characteristics in a large sample of acutely hospitalized older patients. Despite the rather low prevalence of patients reporting pain, the results allow us to

Table 1 Main characteristics at hospital admission of 3577 patients split by their levels of frailty (F0, F1, F2)

	F0 (*n* = 1177)	F1 (*n* = 935)	F2 (*n* = 1169)	Missing
Sex				
Male	620 (52.7)	615 (50.0)	532 (45.5)	
Female	557 (47.3)	616 (50.0)	637 (54.5)	
Age, mean (SD	75.9 (6.9)	78.5 (7.0)	81.5 (7.3)	
65–74	533 (45.3)	378 (30.7)	221 (18.9)	
75–84	497 (42.2)	579 (47.0)	506 (43.3)	
≥ 85	147 (12.5)	274 (22.3)	442 (37.8)	
Geographic area				
North	656 (56.0)	671 (54.7)	725 (62.4)	
Center	216 (18.5)	225 (18.4)	162 (14.0)	
South	298 (25.5)	330 (26.9)	274 (23.6)	
REPOSI year				
2012	385 (32.7)	347 (28.2)	323 (27.6)	
2014	279 (23.7)	261 (21.2)	251 (21.5)	
2016	143 (12.2)	205 (16.6)	203 (17.4)	
2017	210 (17.8)	216 (17.6)	205 (17.5)	
2018	160 (13.6)	202 (16.4)	187 (16.0)	
Living condition				123
Alone	297 (26.1)	308 (26.1)	220 (19.4)	
Family	751 (65.9)	774 (65.5)	719 (63.5)	
Other	43 (3.8)	64 (5.4)	111 (9.8)	
Nursing home	48 (4.2)	36 (3.0)	83 (7.3)	
Pain	251 (21.5)	319 (26.1)	314 (27.2)	29
Duration[a]				109
Acute	146 (62.7)	146 (50.9)	146 (49.2)	
Chronic	87 (37.3)	141 (49.1)	151 (50.8)	
Type[a]				85
Somatic	87 (38.5)	144 (51.1)	169 (58.1)	
Visceral	81 (35.8)	83 (29.4)	68 (23.4)	
Neuropathic	31 (13.7)	38 (13.5)	35 (12.0)	
Other	27 (12.0)	17 (6.0)	19 (6.5)	

Table 1 continued

	F0 (n = 1177)	F1 (n = 935)	F2 (n = 1169)	Missing
Intensity (NRS)[a]				24
Mild (1–3)	73 (30.0)	84 (26.8)	84 (27.4)	
Moderate (4–6)	72 (29.6)	110 (35.0)	93 (30.3)	
Severe (7–10)	96 (39.5)	119 (37.9)	129 (42.0)	
Location[a]				11
Widespread	9 (3.6)	19 (6.0)	20 (6.4)	
1	184 (74.2)	230 (73.0)	216 (69.7)	
2	35 (14.1)	51 (16.2)	53 (17.1)	
≥ 3	20 (8.1)	15 (4.8)	21 (6.8)	
Body site[a]				
Head and neck	20	17	21	
Upper limb[b]	37	40	50	
Trunk[c]	155	187	166	
Lower limb[d]	60	93	104	

Data are expressed as frequencies and percentages (%), unless otherwise specified. Quantile ranges in the definition of the levels of frailty are: [0–0.19] for F0; [0.19–0.32] for F1; [0.32–1] for F2

NRS numeric rating scale

[a] Percentages of pain characteristics (duration, type, intensity, location and body site) refer to 884 patients with pain. Body sites include:

[b] Shoulder, arm, forearm, hand

[c] Thorax, abdomen, beck

[d] Thigh, leg, foot

evaluate how pain and its characteristics are negatively associated with increasing frailty. Only a few studies have previously evaluated the relationship between pain and frailty [18, 19, 26, 27].

Pain and frailty present important differences. Pain, defined by the International Association for the Study of Pain (IASP) as "an unpleasant sensory and emotional experience associated with tissue damage, actual or potential", is a subjective experience, generally considered a symptom of injury or disease. Frailty, on the other hand, is a biological condition derived from multiple clinical factors that indicate a more or less deficient condition of health. Our main finding was the association between chronic but not acute pain and a higher degree of frailty. The definition of chronic pain is still controversial. Typically, pain is considered chronic when it lasts or recurs over a period of more than 3–6 months [28, 29].

According to a more functional concept, chronic pain is triggered and maintained by biochemical and structural changes in the central nervous system, including glial activation and the onset of neuroinflammation, owing to an intense release of nociceptive stimuli over a long period of time [30, 31]. Notably, neuroinflammatory processes can be linked both to

Table 2 Results of ordinal logistic regression models assessing the effect of pain and its characteristics on the degree of frailty (lower frailty as the reference)

		OR (95% CI)
A	Sex (M vs F)	0.92 (0.82–1.05)
	Age (5 years)	1.46 (1.40–1.52)
	Pain (yes vs no)	1.33 (1.15–1.54)
B	Sex (M vs F)	0.93 (0.82–1.05)
	Age (5 years)	1.46 (1.40–1.52)
	Duration (acute vs no)	1.13 (0.93–1.36)
	Duration (chronic vs no)	1.69 (1.38–2.07)
C	Sex (M vs F)	0.93 (0.72–1.25)
	Age (5 years)	1.35 (1.24–1.48)
	Intensity (moderate vs mild)	1.06 (0.77–1.46)
	Intensity (severe vs mild)	1.19 (0.88–1.61)
D	Sex (M vs F)	0.96 (0.73–1.25)
	Age (5 years)	1.40 (1.27–1.54)
	Type (somatic vs other)	1.60 (1.22–2.07)
E	Sex (M vs F)	0.94 (0.73–1.22)
	Age (5 years)	1.38 (1.27–1.51)
	Location (spread vs localized)	1.60 (0.93–2.78)

OR odds ratio, *95% CI* 95% confidence interval

Table 3 Causes of pain in 379 patients with chronic pain[a]

Causes	*N* (%)	*N*
Osteoarthritis	125 (33.6)	
Other musculoskeletal diseases	67 (18.0)	
Spondylitis and column diseases		27
Polymyalgia		22
Rheumatoid arthritis		18
Cancer	53 (14.3)	
Bone diseases	34 (9.1)	
Fractures		22
Osteopathy		12
Diseases with neuropathic components	11 (3.0)	
Other diseases	82 (22.0)	
Diseases of the digestive system		19
Vascular diseases		16
Post-surgical traumas		10
Ulcer		7
Headache		10
Others		20

ICD9-CM codes used in identifying causes of pain: osteoarthritis: 696.0, 715(–719); spondylitis and column diseases: 720–724; rheumatoid arthritis 714; polymyalgia: 710, 725–729; cancer: 140–239, V10; fractures: 733.1–9, 800–821, 905; osteoporosis and other osteopathies: 730–739, excl. 733.1–9; diseases with neuropathic components: 053, 350, 356–357; diseases of the digestive system: 520–579; vascular diseases: 395, 401, 413, 428, 443–444, 446–447, 453–454, 747; ulcer: 707; headache: 307, 784

[a] In seven patients the cause of pain was unknown

chronic pain and to depression, often present in these patients [9].

Persistent pain is typically the consequence of the presence of chronic diseases capable of generating persistent and intense stimuli. In our study, chronic pain was indeed associated with the type of underlying disease.

No significant differences in the frailty index were found between osteoarthritis, cancer and other less frequent diseases causing chronic pain. Exceptions were polymyalgia, rheumatoid arthritis and a few other musculoskeletal diseases, that presented with a lower risk of severe frailty than osteoarthritis (OR = 0.49). Furthermore, widespread rather than localized pain was associated with increasing frailty, and somatic rather than visceral and neuropathic pain was associated with a higher degree of frailty. On the other hand, the frailty index was not influenced by the intensity of pain, ranked as mild, moderate or severe [32, 33]. Surprised by this finding, we chose to evaluate pain intensity separately for chronic pain, but even this analysis failed to show a relationship with the frailty index. This apparent contradiction reinforces the view that the chronicity of pain rather than

Table 4 Results of the ordinal logistic regression model assessing the impact of the main causes of chronic pain on the degree of frailty (lower frailty as the reference) in 372 patients included in the analysis

Variable	OR (95% CI)
Sex (M vs F)	0.95 (0.63–1.41)
Age (5 years)	1.26 (1.10–1.44)
Cause (ref = osteoarthritis)	
Other musculoskeletal diseases	0.49 (0.28–0.85)
Diseases with neuropathic components	1.44 (0.44–4.73)
Bone diseases	0.78 (0.38–1.59)
Other	0.72 (0.42–1.21)
Cancer	1.05 (0.57–1.94)

OR odds ratio, *95% CI* 95% confidence interval

its severity is the main determinant of the degree of frailty.

With regard to pain generators, they were mainly related to chronic conditions strongly connected to chronic inflammatory processes, often widespread with multiple body localizations. Rheumatic diseases and cancer, the most frequent in our cases, are conditions associated with long-lasting and systemic inflammation. The high concentration of pro-inflammatory molecules bind to nociceptors and determine the sustained and continuous presence of painful stimuli, causing on the one hand a situation of permanent and widespread pain and, at the same time, the burden of progressing systemic disease.

In order to break this chain, one goal is to reduce the level of inflammation by means of preventive or therapeutic methods effective for both the cause (inflammation) and the effect (pain) [34].

Because both pain and frailty negatively affect quality of life in older people, better recognition of chronic pain and its management should become a target for intervention that may help to avoid the worsening of frailty in older hospitalized patients.

Limitations

This study on the relationship between pain and frailty was based upon data collected within the framework of a cross-sectional study. Even though the available data allow for an accurate assessment of the frailty index, data on pain and its characteristics are likely to be under-reported, with incomplete information, because its assessment may be hampered when communication problems exist, as is the case in patients with severe cognitive impairment or dementia. A more standardized and specifically-driven data collection method is therefore warranted, and only a prospective study would be able to provide further insights on the natural history of frailty and to assess the potential role of pain as a possible contributor to frailty. Furthermore, at variance with previous reports, we did not take into account physical frailty and characteristics such as weakness and exhaustion. Chronic conditions, such as musculoskeletal diseases and mood disorders, often leading to chronic pain, are also embedded in the definition of the frailty index itself, thus making it difficult to assess how they mediate and modulate the relationship between pain and frailty.

CONCLUSION

Chronic, diffuse and somatic pain associated with long-term chronic diseases is the expression of inflammatory processes, and reasonably affects at least in part the severity of frailty and quality of life in hospitalized older adults with multimorbidity. An accurate and more in-depth evaluation of pain and the recognition of its aetiology may help clinicians to manage these frail patients with effective results.

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Data Availability. The data sets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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