



Research Article

Prevalence and Associated Factors of Frailty in a Cohort of Older People with Opioid use Disorder Receiving Opioid Agonist Therapy

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Abstract

Objective: Frailty is an age-related condition associated with high disability and mortality, however, there is scarce data on frailty in growing aging populations with substance use disorders. The aim of the study was to analyze the prevalence of frailty and related factors in individuals with opioid use disorders. **Methods:** Cross-sectional study including individuals older than 50 years with heroin use disorder on opioid agonist therapy receiving primary care at a drug addiction outpatient center. Frail, pre-frail and robust status were defined according to the Frail scale and severity of comorbidity scored with the CIRS-G (Cumulative Illness Rating-Scale-Geriatrics). **Results:** One hundred and sixty-nine participants were included in the study. Median age was 55 [IQR: 51-58] years and 46(27.2%) were women. Tobacco smoking was present in 160(91.6%) subjects and polysubstance use in 1151(89.2%): cocaine in 149(88.2%), cannabis in 106(62.7%), alcohol in 93(55%). Dual disorders were diagnosed in 48(28.4%) participants. Overall, 101(59.7%) participants had >1 chronic diseases, with a median CIRS-G scoring of 3[IQR:1,5] and were taking a median of 4[IQR:3,6] chronic medications for its treatment. Frailty status was diagnosed in 28(16.6%) individuals, pre-frail in 41(24.2%) and robust in 100(59.2%). Factors associated with frailty and pre-frailty were: age (OR. 1.23; CI: 1.1-1.42, p<0.01) and CIRS-G (OR.5.43; CI: 3.18-9.26, p<0.01). **Conclusions:** Frailty represents a primary health concern in individuals with opioid use disorder, especially among oldest people with high burden of chronic diseases. Given the progressive aging and the high prevalence of chronic diseases, interventions to prevent and treat frailty are necessary in this population.

Keywords: frailty, opioid, chronic diseases, aging, substance use

Introduction

Opioid use disorder [1] (OUD), is a chronic relapsing disease with significant morbidity, including chronic viral infections, overdose, traumatic injuries and premature mortality [2-5]. However, the widespread of preventive public health interventions, especially opioid agonist therapy, has improved the health-related quality of life and survival of people with substance use disorders [6-8]. Among benefits of opioid agonist therapy are included its efficacy in retaining subjects in treatment, decreasing opioid use, risk behaviors related to the hepatitis and HIV infectious diseases, criminal behavior linked to drug consumption and fatal overdose [9,10]. The resulting increase in life expectancy of people with OUD has been accompanied by progressive aging and a growing concern of interest in the study of age-related comorbidity [11-14].

In this sense, frailty is an aging-related syndrome characterized by a decline in the physiological capacity of multiple organ systems, leading to increased vulnerability to stressors events resulting in an increased risk of falls, fractures, hospitalization, institutionalization, impaired quality of life and mortality [15]. Prevalence of frailty among the community-dwelling population aged 65 years and older is about 10% depending on which frailty definitions are used [16]. Frailty may initially be overlooked or incorrectly identified as part of the normal aging process because of the variable nature of the presentation and diagnosis [15-17]. Symptoms include generalized weakness, exhaustion, slow gait, poor balance, decreased physical activity, cognitive impairment, and weight loss [15-17], but the individual's frailty level can be improved through multi-component training exercises [17-19]. There is no current recommendation for frailty routine screening. Frailty is not diagnosed by a single patient-reported symptom or physical examination finding [15], and there are no specific laboratory tests or imaging studies for frailty [20]. Rather, a comprehensive geriatric assessment can identify risk factors and symptoms suggestive of frailty. Suspected clinical frailty should be evaluated using validated frailty diagnosis scale, which classify patients as robust, prefrail, or frail [21].

Frailty is not only consequence of aging, female sex, unhealthy lifestyle, multiple comorbidities, polypharmacy and lower economic status has also been identified as additional risk factors [15-17]. In contrast to the general population, data on frailty are scarce for people with OUD. However, they share several risk factors associated to an accelerating aging, which may suggest a higher prevalence of frailty in this population.

Substance use, especially cocaine and heroin, contributes to aging through multiple pathways, including alterations in oxidative stress, excitotoxicity, mitochondrial dysfunction and telomere

length reduction, which ultimately leading to cell degeneration and apoptosis [22-26]. By contrast, studies have shown reversed association with frailty risk, probably due to reverse causality, residual confounding or survival bias [27-28].

Moreover, people with OUD have a high prevalence of chronic medical conditions [29-31], which are contributing factor to frailty in the general population [31-34]. Age-related diseases and frailty share common risk factors and have a bidirectional relationship with each other. Chronic diseases can contribute as a causal or precipitating factor to the fragile syndrome, while it can lead to greater vulnerability and complications in older adults who suffer from underlying chronic diseases [32,33]. In addition, chronic viral infections, which are more prevalent in people with OUD than general population, have harmful effects on the individual's immune system, exacerbating aging. However, antiretroviral therapy initiation reverses partially the biological aging process and additionally can have some toxicities that influence aging [34].

Understanding potentially modifiable factors that influence the risk of frailty and its progression is a key concern for the management of this urgent contemporary public health challenge. So, it is necessary to carry out studies in people with OUD to promote a healthy aging and improve quality of care. Thus, the aim of this study was to determine the prevalence of frailty and clinical characteristics in a sample of people with opioid use disorder, who received integrated clinical, including medical and psychosocial support, in an outpatient drug addiction center.

Methods

A cross sectional study was conducted in a sample of people with OUD. The former were selected from three outpatient drug treatment centers (CAS: Centro de Atención y Seguimiento a las drogodependencias: Drug Addiction Attention and Follow up Centre) located in or adjoining Barcelona, Spain: CAS Barceloneta, CAS Forum Sant Martí and CAS Santa Coloma. The centers belonged to the public health system and received individuals from two different districts of Barcelona and from the metropolitan area, respectively. Functioning of the centers has been published elsewhere [35].

All those aged >50 years with OUD diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders, Text Revision V criteria, and who had received integrated clinical care, including medical and psychosocial support, at the three drug addiction outpatient centers in 2022 were invited to participate during their routine clinical visits. Participants gave written informed consent.

General characteristics and medical history of the participants were obtained from the medical records. Severity of the comorbidity was assessed through an adapted version of the Cumulative Illness Rating Scale for its use in older patients (CIRS-G)

[36]. The CIRS-G contemplated 14 groups of diseases or categories, evaluating its severity from 0 (no impairment) to 4 (highest possible impairment), giving a final score (score) which was the sum of these evaluations (between 0-56). Low comorbidity was considered for scores 0-2, moderate for 3-8 and high for 9 according to CIRS-G [36]. The FRAIL questionnaire [21] was used to determine frailty and was applied by the center’s physician during routine clinical visits. The FRAIL scale included 5 components: Asthenia, Resistance, Ambulation, Illness, and Loss of weight. Frail scale scores ranged from 0–5 (i.e., 1 point for each component; 0=best to 5=worst) and represented frail (3–5), pre-frail (1–2), and robust (0) health status [21]. For this study, Asthenia was measured by asking respondents how much time during the past 4 weeks they felt tired with responses of “all of the time” or “most of the time” scored 1 point. Resistance was assessed by asking participants if they had any difficulty walking up 10 steps alone without resting and without aids, and Ambulation by asking if they had any difficulty walking several hundred yards alone and without aids; “yes” responses were each scored as 1 point. Illness was scored 1 for respondents who reported 5 or more chronic diseases, excluding psychiatric disorders. Loss of weight was scored 1 for respondents with a weight decline of 5% or greater within the past 12 months.

The primary outcome of the study was the prevalence of frailty among participants. Secondary outcomes were the variables associated with frailty and the prevalence and severity of comorbidity.

Descriptive statistics were expressed as median and inter-quartile range for the quantitative variables, and percentages for the qualitative variables. Means of quantitative variables were compared with the Wilcoxon test. The χ^2 test was used to compare categorical variable proportions.

Logistic regression models were employed to examine the association of clinical variables with FRAIL scores classified as frail or pre-frail vs. robust. Variables included in the analyses were: age, gender, substance use disorder, dual disorders, intravenous use of substances, HIV infection, CIRS-G scoring, time on opioid agonist therapy and total number of medical drug prescriptions. A *p* value < 0.05 was considered significant. Statistical analyses were performed using the free statistical R (3.5.2 version).2.7.

The study was approved by the local ethics committee (2019/8870 CEIC Parc de Salut Mar, Barcelona). All procedures performed in the study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments.

Results

All of 169 adults aged >50 years with OUD who were monitored at the three centers agreed to participate in the study.

Clinical and social characteristics of the participants are shown in (Table 1). Most of the participants were male, middle age Spanish, living at home, unemployed and one third had criminal records.

	Total	Men	Women	<i>p</i>
N	169	123(72.8%)	46(27.2%)	
Age ¹	52(51-58)	54(52,59)	56(53-58)	0.85
Spanish	155(91.7%)	112(91.1%)	43(93.5%)	0.43
Housing (home)	150(88.8%)	112(91.1%)	38(82.65)	0.04
Employment	40(23.7%)	30(24.4%)	10(21.7%)	0.44
Criminal records	59(34.9%)	52(42.3%)	7(15.2%)	<0.01
Dual disorder	48(28.4%)	33(26.8%)	15(32.6%)	0.28
Polydrug use	128(72.2%)	84(71.8%)	40(86.8%)	0.01
Intravenous drug use	143(84.65)	100(81.3%)	43(93.5%)	0.04
Substance use disorder				
Cocaine	149(88.2%)	106(86.2%)	43(93.5%)	0.14
Alcohol	93(55%)	65(52.8%)	28(60.2%)	0.22
Cannabis	106(62.7%)	73(53.9%)	33(71.4%)	0.05
Tobacco	160(91.6%)	118(95.9%)	42(91.3%)	0.77
Time on OAT(years) ¹	27[22,31]	28[20,31]	29[25,32]	0.72

Abstinence	59(34.9%)	45(36.6%)	14(30.4%)	0.28
HIV	40(23.7%)	35(28.5%)	5(10.9%)	0.01
N° chronic diseases				
1	55(32.5%)	40(32.5%)	15(32.6%)	
2	19(11.2%)	13(10.5%)	6(13.1%)	
>3	27(16.1%)	18(14.6%)	9(19.6%)	0.52
CIRS-G ¹ scoring	3(1-5)	4(3,6)	4.5(4,6)	0.25
N.º prescription drugs	4(3,6)	4(3,6)	4(3,8)	0.22
Polypharmacy	73(43.2%)	50(40.6%)	23(50.0%)	0.27
Frailty status				
Robust	100(59.2%)	77(62.6%)	23(50%)	
Pre-frail	41(24.2%)	27(21.8%)	14(30.4%)	0.07
Frail	28(16.6%)	19(15.4%)	9(19.5%)	

Data are presented as No. (%) unless otherwise indicated.1: Data presented as median and interquartile range. Abbreviations: n, number; HIV, human immunodeficiency virus; OAT: opioid agonist therapy; CIRS-G Cumulative Illness Rating Scale-Geriatrics.

Table 1: Social and clinical characteristics of the 169 individuals with opioid use disorder.

One quarter had dual disorders and all the individuals had heroin as the main opioid consumed before seeking treatment. The main mode of substance administration was intravenous and 151(89.2%) had other substance use disorders mainly cocaine, alcohol and cannabis. Women had more intravenous substance and cannabis use compared to men. All the subjects had been on opioid agonist therapy for nearly thirty years and one third remained abstinent. One quarter of the individuals had HIV infection with a median of 483[interquartile range 118-743] cells/mm³ and all had suppressed RNA HIV-1. Three quarters of persons had positive hepatitis C antibodies (immunoglobulin G) but all were on sustained viral response.

One or more chronic medical conditions were determined in more than a half of individuals: chronic respiratory diseases in 61(35.1%), hypertension in 52(30.2%), diabetes in 25(14.8%), chronic liver disease in 24(14.2%), vascular diseases 23(13.6%), cancer 15(8.8%), hypothyroidism 6(3.55) and dementia 3 (1.8%). Half of the participants had moderate or high comorbidity according to CIRS-G and they were taken a median of 4 drugs including opioid agonist therapy.

Frail status was diagnosed in 28 (16.6%; CI95%: 11.0-22.2%) subjects and pre-frailty in 41(24.2%) according to the Frail Scale. Women had a non-significant tendency to higher frail and pre-frail status. Asthenia in 58(33.2%) individuals, low resistance in 39(25.4%), loss of DE ambulation in 39(22.8%), loss of weight in 16(9.4%) and more than 4 chronic diseases in 7 (4.1%) were the most clinical symptoms of frailty. Factors associated with the frailty and pre-frailty are shown in (Table 2). Only age and CIRS-G were associated to frailty in the multivariate analyses.

	Univariate			Multivariate		
	OR	CI 95%	<i>p</i>	OR	CI 95%	<i>p</i>
Age	1.19	1.1-1.29	<0.01	1.23	1.1-1.42	<0.01
Men	0.59	0.3-1.18	0.14			
Dual disorder	0.72	0.3-1.45	0.76			
HIV infection	1.86	0.91-3.81	0.08			
Intravenous drug use	2.07	0.82-5.25	0.12			

Cocaine use	3.09	0.98-9.7	0.05			
Cannabis use	1.19	0.63-2.26	0.57			
Alcohol use	2.03	1.08-3.8	0.03	1.43	0.72-2.84	0.31
Tobacco use	2.5	0.5-12.5	0.25			
Time on OAT	1.01	0.81-1.03	0.59			
Abstinent	1.25	0.65-2.4	0.49			
CIRS-G scoring	4.95	3.1-7.93	<0.01	5.43	3.18-9.26	<0.01
n. ^o prescription drugs	1.31	1.08-2.5	0.01	1.22	0.89-2.5	0.11

Abbreviations: n, number; OR, odds ratio; CI, confidence interval; HIV, human immunodeficiency virus; OAT: opioid agonist therapy; CIRS-G Cumulative Illness Rating Scale-Geriatrics.

Table 2: Multivariate analysis of clinical factors associated to frailty and pre-frailty among 169 individuals with opioid use disorder

Discussion

Although frailty is more common in later life [15], the study showed a noteworthy frailty prevalence of 16.5% in a sample of middle age people with OUD, mainly related to age and severity of chronic diseases. Comparison of frailty prevalence studies is difficult because, in addition to differences in patients included, (community-dwelling people or nursing-home residents), the unequal operative scales of frailty status result in different prevalence between studies [16]. However, recent data from middle age patients residing in the community in European countries using the Frail scale have shown prevalence's ranging from 1.3 to 7.5%; and especially for Spanish population between 4.7%(50-54 years) to 6.7%(55-59 years) in men and 6%(50-54 years) to 6.2%(55-59 years) in women [37].

Along with age, chronic diseases and specifically their severity, were one the factors most associated with frailty in the study. In this regard, the study showed a high prevalence of chronic diseases with approximately 60% of individuals showing one or more conditions, which was a higher rate compared to the general reference population of the same geographical area [38]; and according to data from other cohorts of older patients on methadone therapy [29-31]. It is also important to note the importance of assessing the severity of chronic diseases using comorbidity scales, instead of only analyzing the number of chronic diseases, as they provide additional information about the patient's overall health status [36]. In this way, the study showed that half of the participants with at least one or more chronic diseases had moderate or high comorbidity scoring according to CIRS-G scale, highlighting poor health status and the need for interventions to prevent and reduce the burden of chronic diseases and, thereby, delay the onset of frailty.

Other point of interest of the study was the high prevalence of polypharmacy, especially for those individuals with frailty. It is important, as frailty is associated to increased susceptibility of iatrogenic events, and intensive treatment of chronic diseases may

increase negative health outcomes in frail older adult. Moreover, some treatments and polypharmacy could lead to a frailty [39]. Therefore, the prescribing decision-making process in older people with OUD should be individualized, taking into account frailty and simplifying the number of drugs prescribed as much as possible.

In terms of sex differences, a combination of biological, behavioral and social factors account for the higher frailty scores observed in woman compared to men [15]. In the study women had a tendency to higher frailty prevalence than men, although this trend could not be explained by differences in the number and severity of chronic conditions or age. However, intravenous use was most frequent in women suggesting that addiction severity may play a role in gender differences in frailty risk.

Likewise, the study revealed a high prevalence of other associated substance use disorders, including cocaine, cannabis, alcohol and specially tobacco. However, the study failed to determine the association of each one with frailty. So, studies that analyze the independent impact of these drugs on frailty are needed. This approach is important given that drug use are potentially modifiable risk factors that can identify high-risk populations within people with opioid use disorder who may benefit from preventive interventions, especially for tobacco smoking, which, unlike the other substances, is a well established risk factor for aging and frailty [40].

Finally, the best scale for defining frailty in this specific population has not been established. An assessment of frailty in people with OUD should be simple and not time consuming, because of multiple patient's needs that have to be addressed during routine clinical care, including social, psychological and medical aspects. In this sense, the study showed the feasibility of the Frail scale during their routine clinical care as the first step approach for detecting frailty in a drug addiction center.

The strengths of the present study were the inclusion of a

singular cohort of older adults over 50 years of age with a long history of substance use, as the opioid epidemic in Spain began in the late 1970; and, that chronic diseases were properly diagnosed by a physician at the drug addiction center. However, the observational nature of the study limited casual inferences regarding relationships between substance use and frailty and did not address the dynamic nature of frailty including an individual's possible progression or recovery over time [15-17].

Future longitudinal studies should confirm these results and focus on analyzing clinical consequences of frailty among people with substance use disorders, clarify role of some substances in developing frailty and effectiveness interventions to reverse it.

Conclusion

In conclusion, frailty represents a major health concern in individuals with opioid use disorder, especially in oldest individuals with high burden of comorbidities. Given the projections regarding the progressive aging of these individuals, preventive and therapeutic interventions should be incorporated into clinical practice in order to prevent frailty and future disability. Assessing frailty as part of routine patient's care is mandatory for risk stratification and minimizing poor health outcomes. Potential risk factors, such as alcohol and tobacco smoking should be addressed, as well as an early diagnosis and treatment of chronic diseases. In addition, frailty preventive programs based on exercise and nutrition should be incorporated into health care.

Declaration of Generative AI and AI-assisted technologies:

These have not been used in the preparation and writing of the manuscript.

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