Current HIV Research, 2019, *17*, 204-213

RESEARCH ARTICLE

Frailty among HIV-1 Infected Adults under Antiretroviral Therapy in Indonesia

Wulunggono Wulunggono[1], Evy Yunihastuti[1,*], Hamzah Shatri[1], Edy Rizal Wahyudi[1] and Youdiil Ophinni[2]

[1]*Department of Internal Medicine, Faculty of Medicine, University of Indonesia, Jakarta, Indonesia;* [2]*Department of Pathology, Graduate School of Medicine, Kobe University, Kobe, Japan*

ARTICLE HISTORY

Received: July 10, 2019
Revised: August 12, 2019
Accepted: August 19, 2019

DOI:
10.2174/1570162X17666190828143947

Abstract: ***Background*:** Increasing age of HIV-1 infected population brought about the risk of frailty as comorbidity, whose prevalence is higher in low and middle-income countries (LMICs). Indonesia as an LMIC also bears a major burden of HIV-1 epidemic with a similarly aging population, but the prevalence of frailty and its predictors are unknown.

***Objectives*:** To identify the prevalence of frailty and analyze its associated factors, among HIV-1 infected adults under antiretroviral therapy in Indonesia.

***Methods*:** A cross-sectional study was conducted among HIV-infected individuals with inclusion criteria of age ≥30 years old and underwent ART for at least 6 months. The main assessment was done using Fried's frailty phenotype score, which categorizes subjects into *non-frail*, *pre-frail,* or *frail*. Factors associated with frailty were characterized and multiple logistic regression analysis was performed.

***Results*:** A total of 164 subjects were recruited; male subjects were 118 (72%), the median age was 40.5 years old, and the median CD4 nadir was 53 cells/μl. Frailty was identified among 90 (54.9%) subjects with 84 (51.2%) identified as pre-frail and 6 (3.7%) as frail, with dominant frailty phenotype was weakness in grip strength. The multivariate model showed that depression was the only factor significantly correlated with pre-frailty and frailty (OR 2.14; 95% CI 1.04-4.43, p=0.036).

***Conclusion*:** Frailty is a common occurrence among HIV-infected patients under ART, with depression as an independent predictive factor.

Keywords: HIV-1, AIDS, frailty, antiretroviral therapy, depression, LMIC.

1. INTRODUCTION

The average age of HIV-infected individuals has increased substantially in the past two decades. In 2016, there were 5.7 million people living with HIV (PLHIV) aged 50 years or older globally; 80% of which lived in low- and middle-income countries (LMICs) [1]. These numbers are projected to increase more than double in 2030 [2]. Prolonged life expectancy among HIV-1 infected individuals [3, 4] while reflects the success of antiretroviral therapy (ART) and access to treatment [5, 6] gives rise to a myriad of comorbidities associated with aging [7-12].

One particular concern for older PLHIVs is the increased risk of frailty, defined as a clinical state or a syndrome of increased vulnerability to physiological decline in response to stressors [13, 14]. Phenotypes of frailty were defined by Fried *et al.* using five criteria: unintentional weight loss, exhaustion, reduced physical activity, reduced walking speed, and weakening grip strength [15]. Frailty phenotypes are associated with increased fall incidence, disability, hospitalization, and death in the general population, while pre-frailty a reversible intermediary state between robust and frail is associated with the same outcomes, albeit less pronounced [15-19].

Frailty, among other geriatric syndromes, occurs at a younger age of about 10 years in HIV-1 infected individuals compared to the general population, and HIV is an independent risk factor for frailty [20-24]. Association between HIV-1 infection and frailty may be partly caused by changes in body composition, presenting as central obesity or lipodystrophy, provoked by HIV-1 pathogenesis itself or adverse effects of ART [25-29]. Other independent predictors of frailty among PLHIV were female sex and severe CD4+ cell depletion [30-32], and a persistent frailty phenotype predicted a worse prognosis after ART initiation [33, 34].

*Address correspondence to this author at the Department of Internal Medicine, Faculty of Medicine, University of Indonesia, Jakarta, Indonesia;
Tel: +62811996058; Fax: +62213904546;
E-mail: evy.yunihastuti@gmail.com

1873-4251/19 $58.00+.00

Similar to other LMICs, HIV-1 prevalence in Indonesia is still on the rise due to limited access to treatment 690,000 PLHIV (0.4%) were estimated in 2015, the largest in South-East Asia, and the population of PLHIV is aging [35-38]. Frailty is known to be more prevalent in LMICs [39, 40], while frailty prevalence among Indonesian general population in 2019 was 25.2% [41]; however, practically no data regarding frailty among PLHIV in Indonesia are available. In this study, we aimed to identify the prevalence of frailty and analyze associated factors, among HIV-1 infected adults under ART in Indonesia.

2. MATERIALS AND METHODS

2.1. Study Sample and Data Collection

A cross-sectional study was conducted among HIV-1 infected patients aged 30 years or older, who underwent antiretroviral therapy for at least six months. Exclusion criteria were (1) currently treated for any opportunistic infections, (2) pregnancy, (3) disabilities which hinder physical examination *e.g.* paralysis or mentally ill, and (4) hospitalization within the last two months. Subject recruitment was conducted between September 2018 and January 2019 in HIV Integrated Service Unit of Cipto Mangunkusumo Hospital, Jakarta the national referral center for HIV cases in Indonesia. Questionnaires were administered in the first language of subjects, Bahasa Indonesia.

2.2. Frailty Criteria

Identification of frailty phenotypes was based on five criteria as developed by Fried *et al.* [15]: (1) weight loss, (2) exhaustion, (3) low physical activity, (4) slowness, and (5) weakness (see **Appendix 1**).

Weight loss was defined by 4.5 kilograms loss in body weight in the last year or loss of >5% body weight in the previous year. *Exhaustion* was measured using the two questions: "How often did you feel that every activity that you did are tiring?" and "How often did you feel that you could not do any activity due to your tiredness?" Response options were either none or rarely (<1 day in a week), sometimes (1-2 days), often (3-4 days), or almost always (5-7 days). The criterion was met if subjects answered "often" or "almost always" to any one of the questions. *Low physical activity* was measured using the question, "Did you feel any physical limitation after having done any strenuous activities *e.g.* running or weight lifting?" Response options were either none at all, somewhat limited, or very limited; criterion was met if subjects answered the latter. *Slowness* was objectively measured by walking speed along 15-feet (4.57 m) distance, with average of two measurements was taken. Time of ≥7 s in men with a height of ≤173 cm, or ≥6 s in height of >173 cm, or ≥7 s in women with a height of ≤159 cm, or ≥6 s in height of >159 cm, were defined as slow. *Weakness* of grip strength was also objectively measured using Jamar Hydraulic Hand Dynamometer. Diagnosis of weakness was stratified based on gender and body mass index; in men: ≤29 kg grip strength in BMI ≤24 kg/m^2, or ≤30 kg in 24.1-28 kg/m^2, or ≤32 kg in >28 kg/m^2, while in women: ≤17 kg grip strength in BMI ≤23 kg/m^2, or ≤17.3 kg in 23.1-26 kg/m^2, or ≤18 kg in 26.1-29 kg/m^2, or ≤21 kg in >29 kg/m^2.

Each criterion met was scored as one. Stages of frailty, as defined by Fried *et al.*, were then counted as follows: score of 0 means subject is *robust* or not frail, score of 1-2 means subject is at intermediate risk or considered to be *pre-frail*, and score of 3-5 means that subject is *frail*.

2.3. Independent Variables

To identify risk factors associated with frailty among PLHIV, several socio-demographic, medical history, as well as HIV-1-related variables were included in the analyses of this study: time since HIV-1 diagnosis, nadir CD4 count, BMI, presence of depression, presence and number of co-morbidities, ART regiment, duration of ART, adherence, HIV-1 transmission risk factors, alcohol consumption, marital status, education, and family income. Comorbidities are defined as symptoms not related to acquired immunodeficiency syndrome (AIDS), or also known as non-AIDS defining illnesses; examples of which are diabetes mellitus and cardiovascular diseases. Presence of depression was assessed using the Beck's Depression Inventory-II (BDI-II) [42], which has been translated into Bahasa Indonesia (termed Indo BDI-II) and validated in the general population. Scores above the cut-off point of 17 indicate depression.

2.4. Statistical Analysis

Statistical analyses were performed using SPSS 16.0. Chi-square tests were performed for bivariate analyses of nominal variables with a 2-tailed p-value of <0.05 was considered to be significant. Selected covariates were then included in multivariate analyses using logistic regression.

3. RESULTS

3.1. Baseline Demographics

Of the 164 recruited subjects, 118 (72.0%) were male and the median age was 40.5 years old (Table **1**). Risk factors for HIV were mostly heterosexual transmission (53.7%) followed by injecting drug users (29.9%). Most subjects (75.6%) were clinically diagnosed for HIV more than five years ago, and most (72.6%) have been taking ART for more than five years as well. The most used regiment (70.1%) was non-nucleoside reverse transcriptase inhibitors (NNRTI)-based regiment, and most subjects (74.4%) reported good adherence to therapy, *i.e.* >95% ART taken on schedule for the past three months. Most subjects (81.7%), however, had nadir CD4 count of <200 cells/μl. Hepatitis C coinfection was the most common comorbidity, and 17.7% of subjects presented with 2 or more comorbidities. In terms of body composition, 28.7% of subjects presented with obesity or BMI ≥25kg/m^2.

3.2. Prevalence and Characteristics of Frailty

Frailty assessments were conducted on all subjects. Prevalence of pre-/frailty was 54.9%, of which most (51.2%) were classified into pre-frail and 3.7% were frail. The proportion of pre-/frailty increased in older age: 48.7% in subjects aged 30-39 years old, 57.6% in 40-49, and 66.7% in 50 or older (Fig. **1**).

Table 1. Baseline characteristics.

-	Total (n = 164)	Robust (n= 74)	Pre-frail (n = 84)	Frail (n = 6)	*p* value
Gender, n(%)					
Male	118 (72)	55 (46.6)	58 (49.2)	5 (4.2)	0.624
Age (years), n(%)					
median (IQR)	40.5 (36-47)	-	-	-	-
30 - 39	78 (47.6)	40 (51.3)	34 (43.6)	4 (5.1)	0.309
40 - 49	59 (36)	25 (42.4)	33 (55.9)	1 (1.7)	-
50 - 59	23 (14)	9 (39.1)	13 (56.5)	1 (4.3)	-
≥ 60	4 (2.4)	0 (0)	4 (100)	0 (0)	-
30 - <50	137 (83.5)	65 (47.4)	67 (48.9)	5 (3.6)	0.393
≥50	27 (16.5)	9 (33.3)	17 (63)	1 (3.7)	-
ART, n(%)					
NNRTI-based	115 (70.1)	57 (49.6)	55 (47.8)	3 (2.6)	0.157
PI-based	49 (29.9)	17 (34.7)	29 (59.2)	3 (6.1)	-
Marital status, n(%)					
Married	104 (63.4)	49 (47.1)	52 (50)	3 (2.9)	0.908
Single	37 (22.6)	17 (45.9)	18 (48.6)	2 (5.4)	-
Separated	6 (3.6)	2 (33.3)	4 (66.7)	0 (0)	-
Widow	17 (10.4)	6 (35.3)	10 (58.8)	1 (5.9)	-
Transmission risk factors. n(%)					
Heterosexual	88 (53.7)	40 (44.7)	45 (51.1)	3 (3.4)	0.982
Homosexual	23 (14)	12 (52.2)	11 (47.8)	0 (0)	0.153
Bisexual	8 (4.9)	3 (37.5)	5 (62.5)	0 (0)	0.732
Piercing	13 (7.9)	3 (23.1)	9 (69.2)	1 (7.7)	0.281
Injecting drug users	49 (29.9)	22 (44.9)	23 (46.9)	4 (8.2)	0.127
Education, n(%)					
Elementary or lower	5 (3)	2 (40)	3 (60)	0 (0)	0.049
Junior high	17 (10.4)	5 (29.4)	9 (52.9)	3 (17.6)	-
High school	91 (55.5)	41 (45.1)	47 (51.6)	3 (3.3)	-
University or higher	51 (31.1)	26 (51)	25 (49)	0 (0)	-
Family income, n(%)					
<3.7 million rupiah	82 (50)	34 (41.5)	44 (53.7)	4 (4.9)	0.567
≥3.7 million rupiah	79 (48.2)	38 (48.1)	39 (49.4)	2 (2.5)	-
Time to HIV-1 diagnosis, n(%)					
Median (IQR)	7.6 (5 - 11.8)	-	-	-	-
≥5 years	124 (75.6)	55 (44.4)	64 (51.5)	5 (4)	0.871
<5 years	40 (24.4)	19 (47.5)	20 (50)	1 (2.5)	-

(Table 1) contd….

-	**Total (n = 164)**	**Robust (n= 74)**	**Pre-frail (n = 84)**	**Frail (n = 6)**	***p* value**
ART duration, n(%)					
Median (IQR)	7 (4.5-10.5)	-	-	-	-
≥5 years	119 (72.6)	52 (43.7)	62 (52.1)	5 (4.2)	0.737
<5 years	45 (27.4)	22 (48.9)	22 (48.9)	1 (2.2)	-
ART adherence, n(%)					
Good	122 (74.4)	62 (50.8)	54 (44.3)	6 (4.9)	0.038
History of non adherence	37 (22.6)	11 (29.7)	26 (70.3)	0 (0)	-
Non adherence	5 (3)	1 (20)	4 (80)	0 (0)	-
Alcohol consumption, n(%)					
Often	6 (3.6)	1 (16.7)	4 (66.6)	1 (16.7)	0.157
Rarely	33 (20.1)	16 (48.5)	16 (48.5)	1 (3)	-
Never	125 (76.2)	57 (45.6)	64 (51.2)	4 (3.2)	-
Comorbidities, n(%)					
Diabetes	17 (10.4)	7 (41.2)	10 (58.8)	0 (0)	0.615
Hypertension	16 (9.8)	8 (50)	7 (43.8)	1 (6.2)	0.736
Hepatitis B	10 (6.1)	3 (30)	4 (40)	3 (30)	0.000
Hepatitis C	39 (23.8)	15 (38.5)	21 (53.8)	3 (7.7)	0.241
Lung disease	35 (21.2)	12 (34.3)	20 (57.1)	3 (8.6)	0.111
Others	6 (3.6)	2 (33.3)	4 (66.7)	0 (0)	0.701
Number of comorbidities, n(%)					
0-1 comorbidity	135 (82.3)	64 (47.4)	68 (50.4)	3 (2.2)	0.071
2 comorbidities or more	29 (17.7)	10 (34.5)	16 (55.2)	3 (10.3)	-
Nadir CD4 count, n(%)					
Median (IQR) cells/µl	53 (21–147)	-	-	-	-
<200 cells/µl	134 (81.7)	60 (44.8)	69 (51.5)	5 (3.7)	0.980
>=200 cells/µl	30 (18.3)	14 (46.7)	15 (50)	1 (3.3)	-
Body mass index, n(%)					
Median (IQR) kg/m^2	22.8 (20.4–25.4)	-	-	-	-
<25 kg/m^2	117 (71.3)	57 (48.7)	54 (46.2)	6 (5.1)	0.060
≥25 kg/m^2	47 (28.7)	17 (36.2)	30 (63.8)	0 (0)	-
Depression, n(%)					
No depression (BDI score <17)	120 (73.2)	60 (50)	57 (47.5)	3 (2.5)	0.074
Depression (BDI score ≥17)	44 (26.8)	14 (31.8)	27 (61.4)	3 (6.8)	-

Weakness of grip strength was found in 71.1% of pre-/frailty subjects, which was markedly more common than exhaustion (23.3%), low physical activity (18.9%), weight loss (15.6%), and slow walking speed (6.7%).

3.3. Predictors of Frailty

Out of several risk factors analyzed in this study, as shown in Table **2**, bivariate analysis showed that depression was significantly associated with pre-/frailty (PR 1.36; 95% CI 1.03-4.44, p=0.038). Several covariates were continued into the multivariate model, shown in Table **3**, and it was found that depression also independently predicts the presence of pre-/frailty (OR 2.14; 95% CI 1.04-4.43, p=0.036). No other variables analyzed in this study, including age, nadir CD4 count, comorbidities, and BMI, were associated with frailty phenotype.

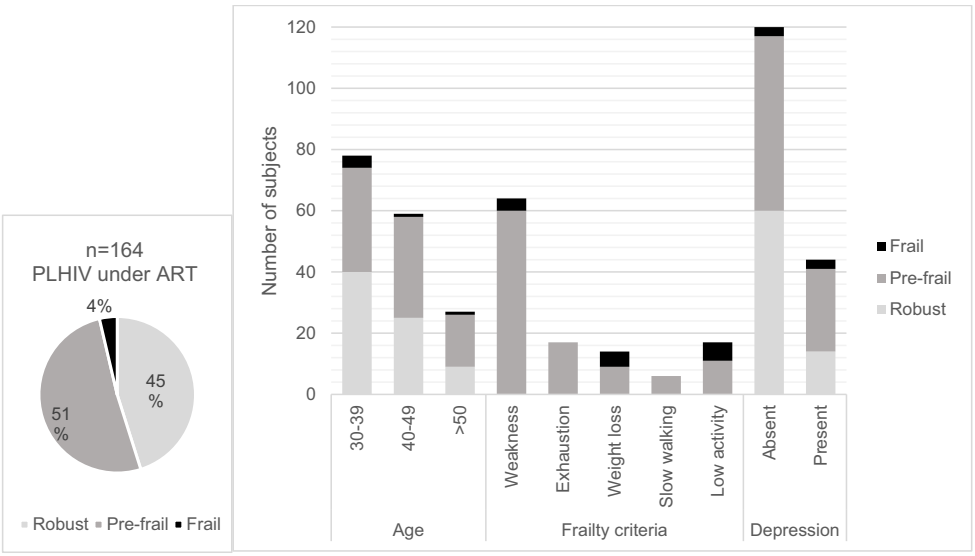

Fig. (1). Prevalence of frailty (*left*) and proportion of frailty, divided by age groups, criteria for frailty phenotypes, and presence of depression (*right*).

Table 2. Bivariate analysis of factors associated to pre-/frailty phenotypes.

Variables	Groups		Prevalence Ratio	95%CI	*p* value
	Pre-/ frail **n (%)**	***Robust*** **n (%)**			
Age (years)					
≥50	18 (66.7)	9 (33.3)	1.26	0.76-4.29	0.178
30 - <50	72 (52.6)	65 (47.4)	-	-	-
Time to HIV-1 diagnosis					
≥5 years	69 (55.6)	55 (44.4)	1.05	0.56-2.32	0.728
<5 years	21 (52.5)	19 (47.5)	-	-	-
ART duration					
≥5 years	67 (56.3)	52 (43.7)	1.10	0.62-2.45	0.551
<5 years	23 (51.1)	22 (48.9)	-	-	-
Nadir CD4 count					
<200 cells/µl	74 (55.2)	60 (44.8)	1.03	0.48-2.38	0.851
≥200 cells/µl	16 (53.3)	14 (46.7)	-	-	-
Comorbidities					
≥2 comorbids	19 (65.5)	10 (34.5)	1.25	0.74-3.95	0.204
0-1 comorbid	71 (52.6)	64 (47.4)	-	-	-
BMI					
≥25 kg/m^2	30 (63.8)	17 (36.2)	1.24	0.84-3.37	0.144
<25 kg/m^2	60 (51.3)	57 (48.7)	-	-	-
Income					
<3.7 million rupiah	48 (58.5)	34 (41.5)	1.12	0.70-2.44	0.397
≥3.7 million rupiah	41 (51.9)	38 (48.1)	-	-	-
Depression					
Depression (BDI score ≥17)	30 (68.2)	14 (31.8)	1.36	1.03-4.44	0.038
No depression (BDI score <17)	60 (50)	60 (50)	-	-	-

Table 3. Multivariate analysis of factors associated to pre-/frailty phenotypes.

Variables	*p**	*p***	OR	95%CI**
Age ≥50 years	0.178	0.217	1.74	0.70-4.19
≥2 Comorbidities	0.204	0.208	1.71	0.91-3.23
BMI ≥25 kg/m^2	0.144	0.161	1.64	0.87-3.69
Depression (BDI score ≥17)	**0.038**	**0.036**	**2.14**	**1.034-4.43**

* in bivariate analysis, ** in multivariate analysis

4. DISCUSSION

4.1. Prevalence of Frailty and Associated Factors

Fried *et al.* introduced the frailty phenotype concept as aging comorbidity, where 7% of individuals over 65 years and as many as 26% over 80 years experienced frail [15]. The concept was adapted and applied in subsequent studies into HIV-1 infected population, in which frail was found in 5-19% of PLHIV in various age groups [21, 30, 31, 43].

In this study, criteria for frail were established in 3.7% of subjects and pre-frail in 51.2%. A study in South Africa recruited similar age groups as of our study [31], but the prevalence of frailty was found to be higher: 49.2% pre-frail and 19.4% frail. The same study, however, also recruited ART-naïve subjects that may skew clinical presentation of subjects. Other differences in demographics, *e.g.* higher proportion of women [30], may also explain the difference. Characteristic of censused PLHIV in Indonesia itself is leaning towards male in a 2:1 ratio [44], and the consecutive sampling nature of our study gives an output of more men included as subjects.

Pre-frail category as measured by Fried criteria represents intermediate-risk towards frail and associated negative outcomes, *e.g.* fall incidence and hospitalization. Frailty is known to occur earlier in PLHIV compared to the general population [21-23], and thus it is of benefit to recognize the pre-frail condition in PLHIV, even in younger age groups. Fig. (**1**) shows increased proportion of pre-frail as age increases, and more than half of 40-49 years old age group had at least one frailty phenotype. Similar results were shown by Kooij *et al.*, where proportion of pre-frail and frail showed upward trends as age increases, in both HIV positive and negative subjects [25].

Frailty, as defined by Fried, only considered the physical condition and does not take cognitive or psychological factors into account. Exclusion of both factors is a matter of debate, as they are well known as important contributors to geriatric disability; indeed, newer definition *e.g.* the frailty index (FI) by Rockwood included both domains [45, 46]. Depression the most frequent psychiatric disease including in PLHIV [47, 48] is 2-3 times higher in PLHIV than in the general population and has been implicated in decreased physical strength, work productivity, and social ability in aging individuals [49, 50]. In this study, depression was screened using the Indonesian version of Beck's Depression Inventory-II (BDI-II) [42]. Out of all subjects with depression, 68.2% of them belong to frailty group; multivariate analysis as shown in Table **3** also confirmed depression as an independent predictor of frailty. A study by Kooij *et al.* assessed for depression albeit with different instrument and found that 26.4% of subjects in the HIV positive group belonged to pre-frail and frail groups [25]. A study by Rees *et al.* also concluded that depression is strongly associated with frailty in HIV-infected patients [51]. These reports warrant further consideration into the impact of depression and psychological factors toward a physical condition in the aging population of PLHIV.

Our results also implicated that neurocognitive assessment linking to frailty in PLHIV is mandatory, as depression is closely associated with HIV-associated neurocognitive disorder (HAND) [52-54]. Indeed, cognitive impairment was found to be more common among frail (59%) compared to non-frail (34%) individuals, both of which predict poor outcomes [55, 56]. In Indonesia, the prevalence of HAND was 51% among treatment-naïve PLHIV but cognitive function improved and stabilized after 6 months of ART [57, 58]. Nevertheless, presence of dementia and cognitive function was not assessed in this study, which we acknowledge as an important limitation of the study.

Presence of comorbidity is closely related to the deteriorating physical condition of PLHIV and may become signs of progression towards frailty. In this study, the most common comorbidity found was hepatitis C. In line with a previous study by Önen *et al.*, hepatitis C was also identified as the most prevalent comorbidity, indicating that pro-inflammatory state caused by HIV-hepatitis C co-infection may clinically manifest as physical frailty [55]. Aging comorbidities *e.g.* metabolic and cardiovascular diseases, however, were not identified as predictors in this study, partly due to low incidence as younger age groups were recruited.

Several studies have identified low CD4 count as a strong independent predictor to frailty, and CD4 count of less than 100 cells/μl is correlated to slower gait and lower grip strength [21, 30]. In this study, most subjects had nadir CD4 count of less than 200 cells/μl, but no association to frailty were found. Similar results were also shown by Kooij *et al.* and Petit *et al.*, in which CD4 count (both nadir and current) showed no correlation to frailty phenotypes [25, 59]. In this study, we could only pick nadir CD4 for analysis, which is not enough to illustrate immune status of subjects and their progression. Laboratory monitoring for HIV is not covered by Indonesian national health insurance, so tests including CD4 are self-reliant, heavily limiting the frequency of CD4 measurements by PLHIV to once a year or less. A better way to represent immune progression might be the cumulative duration of CD4 <200 which correlated to frailty in a study

by Kooij *et al.* [25]; nevertheless, due to the lack of measurement in our subjects, our CD4 data is unreliable. Another point worth mentioning is that our analysis combined frailty and prefrailty as outcome; other studies with similar methodology [25, 59] showed non-association to CD4 status.

Earlier onset of frailty among PLHIV was considered to be related to pathologic changes in body composition, such as central obesity and lipodystrophy [26]. Our findings, however, showed no correlation between BMI and frailty outcomes. Alternatively, even though grip weakness and fatigue were the more dominant phenotypes in pre-frail group, frail group showed signs of weight loss and low physical activity, indicating that muscle wasting has occurred in frail condition. Muscle mass and presence of sarcopenia, however, were not assessed in this study, which left any link between frailty and muscle composition unexplored. Changes in fat and/or muscle composition may be caused by wasting syndrome associated with AIDS itself or adverse effect of ART, *e.g.* stavudine [29, 60-62]. Stavudine use, however, has been tapered off in Indonesia in the last decade due to toxicity [63, 64], and our analysis failed to show any association between ART regiment as a covariate to frailty phenotype.

Socioeconomic factors have been known to contribute to frailty, and frailty prevalence itself is higher in LMICs than in higher-income countries [39, 65], but the causal directionality remains unclear. Worsening of physical strength may lessen the ability to work and heighten risk of economic difficulties, which may lead to inability to pay for health insurance and poor nutritional intake, leading to frailty [39, 65]. This study, however, did not show any correlation between family income and frailty. Other similar studies also did not show any association between socioeconomic and education status to frailty [25, 55, 59] and it is likely that other unaccounted socioeconomic covariates such as economic balance and perception of financial well-being *i.e.* quality of life [66-68], plays a more important role.

4.2. Strength and Limitation

This study was the first to determine the proportion and associated factors of the pre-frail and frail condition in HIV-1 infected individuals in Indonesia. We also objectively measured frailty phenotypes instead of self-reporting methods that are prone to bias. In addition, we also identified the proportions of pre-frail and frail in younger age groups of PLHIV, many of whom experienced pre-frail and are at risk to progress further into frail phenotypes.

Cross-sectional study design, however, lacks the ability to establish any causal or temporal relationship between HIV-1-related risk factors and frailty, as well as frailty and associated outcomes, such as falls and disability. Being in a resource-limited setting, reliable datasets of CD4 count among other potential HIV-related risk factors, *e.g.* plasma viral load, were unavailable. Complete physical measurement, *e.g.* waist-hip circumference and bioelectrical impedance, may further elucidate the link between fat, muscle composition, and frailty.

Frailty phenotype as defined by Fried the most used measurement in frailty studies [69] only accounts for the physical condition of subjects, while neurocognitive and psychosocial aspects remain unassessed. Inclusion of BDI-II may help to indicate presence of depression, but thorough assessment of these two domains, preferably using the more comprehensive FI [45, 46], is warranted in frailty studies. An investigation into neurocognitive loss and HAND Inclusion of socioeconomic variables known to affect frailty *e.g.* quality of life [68, 70], may also shed further light into predictive factors of frailty among PLHIV.

CONCLUSION

We identified frailty and associated risk factors among PLHIV under ART in Indonesia, of which frailty is a common occurrence. Depression was identified as an independent predictive factor to frailty, warranting further consideration into the mental health of aging PLHIV. It is imperative that longitudinal cohorts be conducted to further analyze frailty and predictive factors among PLHIV, particularly in LMICs.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Ethics Committee of the Faculty of Medicine, University of Indonesia, Indonesia, (0702/UN2.F1/ETIK/2018).

HUMAN AND ANIMAL RIGHTS

No animals were used in this research. All humans research procedures were in accordance with the standards set forth in the Declaration of Helsinki principles of 1975, as revised in 2013 (http://ethics.iit.edu/ecodes/node/3931).

CONSENT FOR PUBLICATION

Written informed consents were obtained from all recruited subjects.

AVAILABILITY OF DATA AND MATERIALS

Datasets used in this study are available from the corresponding author (EY) upon request.

FUNDING

This study was funded by the PITTA grant awarded by the University of Indonesia, Jakarta, Indonesia, grant no. 2074/UN2.R3.1/HKP.05.00/2018.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

AUTHOR CONTRIBUTIONS

WW, EY, HS, and EDW planned the study. WW and EY contributed to acquisition of data. WW, EY, HS, EDW, and

YO contributed to analysis and interpretation of data. WW and YO wrote the manuscript. All authors read and approved the final manuscript.

Appendix 1. Criteria for frailty phenotype.

Criteria	Definition
Weight loss	>10 pounds unintentional weight loss in last year or ≥5% of previous year's body weight
Exhaustion	Subjects answering 2 or 3 to either one of two questions, "How often in the last week have you felt that:" Everything you did was an effort or You could not get going 0 = rarely or none of the time (<1 day) 1 = some or a little of the time (1-2 days) 2 = a moderate amount of the time (3-4 days) 3 = most of the time
Low physical activity	Subjects answering 3 to the questions, "Does your health limits your ability to do strenuous activities, e.g. running or weight lifting?" 1 = not at all 2 = somewhat limited 3 = very limited
Slow walking time	Stratified by gender and height: *Men; cut-off for time to walk 15 feet* Height ≤173 cm; ≥7 seconds Height >173 cm; ≥6 seconds *Women; cut-off for time to walk 15 feet* Height ≤159 cm; ≥7 seconds Height >159 cm; ≥6 seconds
Weak grip strength	Stratified by gender and body mass index (BMI) quartiles: *Men; cut-off for grip strength* BMI ≤24; ≤29 kg BMI 24.1–26; ≤30 kg BMI 26.1–28; ≤30 kg BMI >28; ≤32 kg *Women; cut-off for grip strength* BMI ≤23; ≤17 kg BMI 23.1–26; ≤17.3 kg BMI 26.1–29; ≤18 kg BMI >29; ≤21 kg

REFERENCES

[1] Autenrieth CS, Beck EJ, Stelzle D, Mallouris C, Mahy M, Ghys P. Global and regional trends of people living with HIV aged 50 and over: Estimates and projections for 2000-2020. PLoS One 2018; 13(11): e0207005. [http://dx.doi.org/10.1371/journal.pone.0207005] [PMID: 30496302]

[2] Smit M, Brinkman K, Geerlings S, *et al.* ATHENA observational cohort. Future challenges for clinical care of an ageing population infected with HIV: a modelling study. Lancet Infect Dis 2015; 15(7): 810-8. [http://dx.doi.org/10.1016/S1473-3099(15)00056-0] [PMID: 26070969]

[3] Nakagawa F, Lodwick RK, Smith CJ, *et al.* Projected life expectancy of people with HIV according to timing of diagnosis. AIDS 2012; 26(3): 335-43. [http://dx.doi.org/10.1097/QAD.0b013e32834dcec9] [PMID: 22089374]

[4] Nakagawa F, May M, Phillips A. Life expectancy living with HIV: recent estimates and future implications. Curr Opin Infect Dis 2013; 26(1): 17-25. [http://dx.doi.org/10.1097/QCO.0b013e32835ba6b1] [PMID: 23221765]

[5] UNAIDS. Global HIV/AIDS statistics: 2018 fact sheet [Internet]. 2018. Available from: . http://www.unaids.org/En/Resources/Fact-Sheet

[6] Saag MS, Benson CA, Gandhi RT, *et al.* Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2018 recommendations of the international antiviral society-USA panel. JAMA 2018; 320(4): 379-96. [http://dx.doi.org/10.1001/jama.2018.8431] [PMID: 30043070]

[7] Justice AC. HIV and aging: Time for a new paradigm. Curr HIV/AIDS Rep 2010; 7(2): 69-76. [http://dx.doi.org/10.1007/s11904-010-0041-9] [PMID: 20425560]

[8] Justice A, Falutz J. Aging and HIV: An evolving understanding. Curr Opin HIV AIDS 2014; 9(4): 291-3. [http://dx.doi.org/10.1097/COH.0000000000000081] [PMID: 24871091]

[9] Deeks SG. HIV infection, inflammation, immunosenescence, and aging. Annu Rev Med 2011; 62(1): 141-55. [http://dx.doi.org/10.1146/annurev-med-042909-093756] [PMID: 21090961]

[10] Hasse B, Ledergerber B, Furrer H, *et al.* Swiss HIV Cohort Study. Morbidity and aging in HIV-infected persons: The Swiss HIV cohort study. Clin Infect Dis 2011; 53(11): 1130-9. [http://dx.doi.org/10.1093/cid/cir626] [PMID: 21998280]

[11] Cardoso SW, Torres TS, Santini-Oliveira M, Marins LMS, Veloso VG, Grinsztejn B. Aging with HIV: A practical review. Braz J Infect Dis 2013; 17(4): 464-79. [http://dx.doi.org/10.1016/j.bjid.2012.11.007] [PMID: 23711587]

[12] Wing EJ. HIV and aging. Int J Infect Dis 2016; 53: 61-8. [http://dx.doi.org/10.1016/j.ijid.2016.10.004] [PMID: 27756678]

[13] Morley JE, Vellas B, van Kan GA, *et al.* Frailty consensus: A call to action. J Am Med Dir Assoc 2013; 14(6): 392-7. [http://dx.doi.org/10.1016/j.jamda.2013.03.022] [PMID: 23764209]

[14] Chen X, Mao G, Leng SX. Frailty syndrome: An overview. Clin Interv Aging 2014; 9: 433-41. [PMID: 24672230]

[15] Fried LP, Tangen CM, Walston J, *et al.* Frailty in older adults: evidence for a phenotype. J Gerontol Ser A Biol Sci Med Sci 2001; 56(3): M146-56. [https://doi.org/10.1093/gerona/56.3.m146] [PMID: 11253156]

[16] Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. Lancet 2013; 381(9868): 752-62. [http://dx.doi.org/10.1016/S0140-6736(12)62167-9] [PMID: 23395245]

[17] Fried LP, Ferrucci L, Darer J, Williamson JD, Anderson G. Untangling the concepts of disability, frailty, and comorbidity: Implications for improved targeting and care. Journals Gerontol Ser A Biol Sci. Med Sci 2004; 59(3): M255-63.

[18] Op het Veld LPM, van Rossum E, Kempen GIJM, de Vet HCW, Hajema K, Beurskens AJHM. Fried phenotype of frailty: Cross-sectional comparison of three frailty stages on various health domains. BMC Geriatr 2015; 15(1): 77. [http://dx.doi.org/10.1186/s12877-015-0078-0] [PMID: 26155837]

[19] Xue QL. The frailty syndrome: definition and natural history. Clin Geriatr Med 2011; 27(1): 1-15. [http://dx.doi.org/10.1016/j.cger.2010.08.009] [PMID: 21093718]

[20] Greene M, Covinsky KE, Valcour V, *et al.* Geriatric syndromes in older HIV-infected adults. J Acquir Immune Defic Syndr 2015; 69(2): 161-7. [http://dx.doi.org/10.1097/QAI.0000000000000556] [PMID: 26009828]

[21] Desquilbet L, Jacobson LP, Fried LP, *et al.* Multicenter AIDS Cohort Study. HIV-1 infection is associated with an earlier occurrence of a phenotype related to frailty. J Gerontol A Biol Sci Med Sci 2007; 62(11): 1279-86. [http://dx.doi.org/10.1093/gerona/62.11.1279] [PMID: 18000149]

[22] Schouten J, Wit FW, Stolte IG, *et al.* AGEhIV Cohort Study Group. Cross-sectional comparison of the prevalence of age-associated comorbidities and their risk factors between HIV-infected and uninfected individuals: the AGEhIV cohort study. Clin Infect Dis 2014; 59(12): 1787-97. [http://dx.doi.org/10.1093/cid/ciu701] [PMID: 25182245]

[23] Brothers TD, Kirkland S, Guaraldi G, *et al.* Frailty in people aging with human immunodeficiency virus (HIV) infection. J Infect Dis 2014; 210(8): 1170-9. [http://dx.doi.org/10.1093/infdis/jiu258] [PMID: 24903667]

[24] Levett TJ, Cresswell FV, Malik MA, Fisher M, Wright J. Systematic review of prevalence and predictors of frailty in individuals with human immunodeficiency virus. J Am Geriatr Soc 2016; 64(5): 1006-14. [http://dx.doi.org/10.1111/jgs.14101] [PMID: 27225356]

[25] Kooij KW, Wit FWNM, Schouten J, *et al.* AGEhIV Cohort Study Group. HIV infection is independently associated with frailty in middle-aged HIV type 1-infected individuals compared with similar but uninfected controls. AIDS 2016; 30(2): 241-50. [http://dx.doi.org/10.1097/QAD.0000000000000910] [PMID: 26684821]

[26] Shah K, Hilton TN, Myers L, Pinto JF, Luque AE, Hall WJ. A new frailty syndrome: Central obesity and frailty in older adults with the human immunodeficiency virus. J Am Geriatr Soc 2012; 60(3): 545-9. [http://dx.doi.org/10.1111/j.1532-5415.2011.03819.x] [PMID: 22315957]

[27] Stanley TL, Grinspoon SK. Body composition and metabolic changes in HIV-infected patients. J Infect Dis 2012; 205(Suppl. 3): S383-90. [http://dx.doi.org/10.1093/infdis/jis205] [PMID: 22577212]

[28] McComsey GA, Moser C, Currier J, *et al.* Body composition changes after initiation of raltegravir or protease inhibitors: ACTG A5260s. Clin Infect Dis 2016; 62(7): 853-62. [http://dx.doi.org/10.1093/cid/ciw017] [PMID: 26797215]

[29] Erlandson KM, Wu K, Koletar SL, *et al.* Association between frailty and components of the frailty phenotype with modifiable risk factors and antiretroviral therapy. J Infect Dis 2017; 215(6): 933-7. [http://dx.doi.org/10.1093/infdis/jix063] [PMID: 28453849]

[30] Terzian AS, Holman S, Nathwani N, *et al.* Women's Interagency HIV Study. Factors associated with preclinical disability and frailty among HIV-infected and HIV-uninfected women in the era of cART. J Womens Health (Larchmt) 2009; 18(12): 1965-74. [http://dx.doi.org/10.1089/jwh.2008.1090] [PMID: 20044858]

[31] Pathai S, Gilbert C, Weiss HA, *et al.* Frailty in HIV-infected adults in South Africa. J Acquir Immune Defic Syndr 2013; 62(1): 43-51. [http://dx.doi.org/10.1097/QAI.0b013e318273b631] [PMID: 23018372]

[32] Desquilbet L, Margolick JB, Fried LP, *et al.* Multicenter AIDS Cohort Study. Relationship between a frailty-related phenotype and progressive deterioration of the immune system in HIV-infected men. J Acquir Immune Defic Syndr 2009; 50(3): 299-306. [http://dx.doi.org/10.1097/QAI.0b013e3181945eb0] [PMID: 19194312]

[33] Desquilbet L, Jacobson LP, Fried LP, Phair JP, Jamieson BD, Holloway M, *et al.* A frailty-related phenotype before HAART initiation as an independent risk factor for AIDS or death after HAART among HIV-infected men Journals Gerontol - Ser A Biol Sci Med Sci 2011; 66A(9): 1030-8.

[34] Guaraldi G, Brothers TD, Zona S, *et al.* A frailty index predicts survival and incident multimorbidity independent of markers of HIV disease severity. AIDS 2015; 29(13): 1633-41. [http://dx.doi.org/10.1097/QAD.0000000000000753] [PMID: 26372273]

[35] UNAIDS. Indonesia [Internet]. UNAIDS. 2016. Available from: https://www.unaids.org/en/regionscountries/countries/indonesia

[36] Indonesian Health Ministry. Situasi penyakit HIV AIDS di Indonesia [Internet]. Pusat Data dan Informasi Kementerian Kesehatan Republik Indonesia. 2016. pp. 1–8. Available from: http://www.depkes.go.id/resources/download/pusdatin/infodatin/infodatin hive aids.pdf

[37] Pendse R, Gupta S, Yu D, Sarkar S. HIV/AIDS in the South-East Asia region: progress and challenges. J Virus Erad 2016; 2(Suppl. 4): 1-6. [PMID: 28303199]

[38] The World Bank. New Country Classifications | Data [Internet]. The World Bank Group. 2019. Available from: http://data.worldbank.org/news/new-country-classifications

[39] Siriwardhana DD, Hardoon S, Rait G, Weerasinghe MC, Walters KR. Prevalence of frailty and prefrailty among community-dwelling older adults in low-income and middle-income countries: a systematic review and meta-analysis. BMJ Open 2018; 8(3): e018195. [http://dx.doi.org/10.1136/bmjopen-2017-018195] [PMID: 29496895]

[40] Gray WK, Richardson J, McGuire J, *et al.* Frailty screening in low- and middle-income countries: A systematic review. J Am Geriatr Soc 2016; 64(4): 806-23. [http://dx.doi.org/10.1111/jgs.14069] [PMID: 27100577]

[41] Setiati S, Laksmi PW, Aryana IGPS, *et al.* Frailty state among Indonesian elderly: prevalence, associated factors, and frailty state transition. BMC Geriatr 2019; 19(1): 182. [http://dx.doi.org/10.1186/s12877-019-1198-8] [PMID: 31269921]

[42] Beck AT, Steer RA, Brown KG. Manual for the Beck Depression Inventory-IISan Antonio, TX Psychol Corp. 1996; 60: pp. 239-51.

[43] Önen NF, Agbebi A, Shacham E, Stamm KE, Önen AR, Overton ET. Frailty among HIV-infected persons in an urban outpatient care setting. J Infect 2009; 59(5): 346-52. [http://dx.doi.org/10.1016/j.jinf.2009.08.008] [PMID: 19706308]

[44] Indonesian Health Ministy. Laporan perkembangan HIV AIDS &infeksi menular seksual tahun 2018 [Internet]. Kementerian Kesehatan Republik Indonesia. 2018. pp. 1-158. Available from: http://siha.depkes.go.id/portal/files_upload/Laporan_Triwulan_IV_2018.pdf

[45] Jones DM, Song X, Rockwood K. Operationalizing a frailty index from a standardized comprehensive geriatric assessment. J Am Geriatr Soc 2004; 52(11): 1929-33. [http://dx.doi.org/10.1111/j.1532-5415.2004.52521.x] [PMID: 15507074]

[46] Searle SD, Mitnitski A, Gahbauer EA, Gill TM, Rockwood K. A standard procedure for creating a frailty index. BMC Geriatr 2008; 8: 24. [http://dx.doi.org/10.1186/1471-2318-8-24] [PMID: 18826625]

[47] Richards D. Prevalence and clinical course of depression: a review. Clin Psychol Rev 2011; 31(7): 1117-25. [http://dx.doi.org/10.1016/j.cpr.2011.07.004] [PMID: 21820991]

[48] Nanni MG, Caruso R, Mitchell AJ, Meggiolaro E, Grassi L. Depression in HIV infected patients: a review. Curr Psychiatry Rep 2015; 17(1): 530. [http://dx.doi.org/10.1007/s11920-014-0530-4] [PMID: 25413636]

[49] Ciesla JA, Roberts JE. Meta-analysis of the relationship between HIV infection and risk for depressive disorders. Am J Psychiatry 2001; 158(5): 725-30. [http://dx.doi.org/10.1176/appi.ajp.158.5.725] [PMID: 11329393]

[50] Arseniou S, Arvaniti A, Samakouri M. HIV infection and depression. Psychiatry Clin Neurosci 2014; 68(2): 96-109. [http://dx.doi.org/10.1111/pcn.12097] [PMID: 24552630]

[51] Rees HC, Meister E, Mohler MJ, Klotz SA. HIV-related frailty Is not characterized by sarcopenia. J Int Assoc Provid AIDS Care 2016; 15(2): 131-4. [http://dx.doi.org/10.1177/2325957414553848] [PMID: 25320145]

[52] McIntosh RC, Seay JS, Antoni MH, Schneiderman N. Cognitive vulnerability for depression in HIV. J Affect Disord 2013; 150(3): 908-15. [http://dx.doi.org/10.1016/j.jad.2013.05.014] [PMID: 23726660]

[53] Watkins CC, Treisman GJ. Cognitive impairment in patients with AIDS - prevalence and severity. HIV AIDS (Auckl) 2015; 7: 35-47.

[http://dx.doi.org/10.2147/HIV.S39665] [PMID: 25678819]

[54] Bragança M, Palha A. Depression and neurocognitive performance in Portuguese patients infected with HIV. AIDS Behav 2011; 15(8): 1879-87.
[http://dx.doi.org/10.1007/s10461-011-9973-3] [PMID: 21598031]

[55] Önen NF, Patel P, Baker J, *et al.* Frailty and pre-frailty in a contemporary cohort of HIV-infected adults. J Frailty Aging 2014; 3(3): 158-65.
[PMID: 27050062]

[56] Erlandson KM, Perez J, Abdo M, *et al.* Frailty, neurocognitive impairment, or both in predicting poor health outcomes among adults living with human immunodeficiency virus. Clin Infect Dis 2019; 68(1): 131-8.
[http://dx.doi.org/10.1093/cid/ciy430] [PMID: 29788039]

[57] Estiasari R, Imran D, Lastri DN, Prawirohardjo P, Price P. Cognitive impairment among Indonesia HIV naïve patients. Neurol Asia 2015; 20(2): 155-60.

[58] Estiasari R, Aryanto I, Lee S, Pramana S, Djauzi S, Price P. Determinants of cognitive health in Indonesian HIV patients beginning antiretroviral therapy. J Neurovirol 2019; [Epub ahead of print].
[http://dx.doi.org/10.1007/s13365-019-00787-2] [PMID: 31385196]

[59] Petit N, Enel P, Ravaux I, *et al.* Visage group. Frail and pre-frail phenotype is associated with pain in older HIV-infected patients. Medicine (Baltimore) 2018; 97(6): e9852.
[http://dx.doi.org/10.1097/MD.0000000000009852] [PMID: 29419697]

[60] Bartlett JG. Weight loss and wasting in patients infected with human immunodeficiency virus. Infect Dis Clin Pract 2004; 12(2): 128.

[61] Dudgeon WD, Phillips KD, Carson JA, Brewer RB, Durstine JL, Hand GA. Counteracting muscle wasting in HIV-infected individuals. HIV Med 2006; 7(5): 299-310.
[http://dx.doi.org/10.1111/j.1468-1293.2006.00380.x] [PMID: 16945075]

[62] McComsey GA, Lo Re V III, O'Riordan M, *et al.* Effect of reducing the dose of stavudine on body composition, bone density, and markers of mitochondrial toxicity in HIV-infected subjects: a randomized, controlled study. Clin Infect Dis 2008; 46(8): 1290-6.
[http://dx.doi.org/10.1086/529384] [PMID: 18444869]

[63] Octaviana F, Safri AY, Setiawan DD, *et al.* Neuropathic pain in HIV patients receiving ART without stavudine in an Indonesia Referral Hospital. J Neurol Sci 2019; 397: 146-9.
[http://dx.doi.org/10.1016/j.jns.2018.12.041] [PMID: 30634130]

[64] Tang MW, Rhee SY, Bertagnolio S, *et al.* Nucleoside reverse transcriptase inhibitor resistance mutations associated with first-line stavudine-containing antiretroviral therapy: programmatic implications for countries phasing out stavudine. J Infect Dis 2013; 207(Suppl. 2): S70-7.
[http://dx.doi.org/10.1093/infdis/jit114] [PMID: 23687292]

[65] Gomes CDS, Guerra RO, Wu YY, *et al.* Social and economic predictors of worse frailty status occurrence across selected countries in North and South America and Europe. Innov Aging 2018; 2(3): igy037.
[http://dx.doi.org/10.1093/geroni/igy037] [PMID: 30569024]

[66] Lamu AN, Olsen JA. The relative importance of health, income and social relations for subjective well-being: An integrative analysis. Soc Sci Med 2016; 152: 176-85.
[http://dx.doi.org/10.1016/j.socscimed.2016.01.046] [PMID: 26854627]

[67] Max-Neef M. Economic growth and quality of life: a threshold hypothesis. Ecol Econ 1995; 15(2): 115-8.
[http://dx.doi.org/10.1016/0921-8009(95)00064-X]

[68] Rizzoli R, Reginster JY, Arnal JF, *et al.* Quality of life in sarcopenia and frailty. Calcif Tissue Int 2013; 93(2): 101-20.
[http://dx.doi.org/10.1007/s00223-013-9758-y] [PMID: 23828275]

[69] Bouillon K, Kivimaki M, Hamer M, *et al.* Measures of frailty in population-based studies: an overview. BMC Geriatr 2013; 13(1): 64.
[http://dx.doi.org/10.1186/1471-2318-13-64] [PMID: 23786540]

[70] Felce D, Perry J. Quality of life: its definition and measurement. Res Dev Disabil 1995; 16(1): 51-74.
[http://dx.doi.org/10.1016/0891-4222(94)00028-8]