

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



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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/ μ l. 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.

ARTICLE HISTORY

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

DOI:
10.2174/1570162X17666190828143947



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].

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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-foot (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/m², or ≤ 30 kg in 24.1-28 kg/m², or ≤ 32 kg in >28 kg/m², while in women: ≤ 17 kg grip strength in BMI ≤ 23 kg/m², or ≤ 17.3 kg in 23.1-26 kg/m², or ≤ 18 kg in 26.1-29 kg/m², or ≤ 21 kg in >29 kg/m².

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 comorbidities, ART regimen, 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 regimen (70.1%) was non-nucleoside reverse transcriptase inhibitors (NNRTI)-based regimen, 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/ μ l. 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 ≥ 25 kg/m².

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.

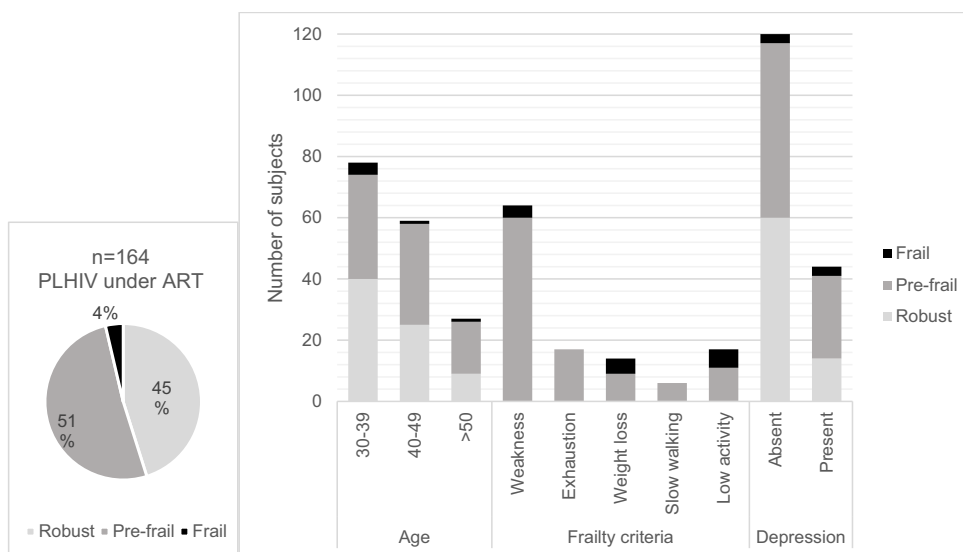


Fig. (1). Prevalence of frailty (*left*) and proportion of frailty, divided by age groups, criteria for frailty phenotypes, and presence of depression (*right*).

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	<i>p</i> *	<i>p</i> **	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 regimen 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 $\geq 5\%$ 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: <i>Men; cut-off for time to walk 15 feet</i> Height ≤ 173 cm; ≥ 7 seconds Height > 173 cm; ≥ 6 seconds <i>Women; cut-off for time to walk 15 feet</i> Height ≤ 159 cm; ≥ 7 seconds Height > 159 cm; ≥ 6 seconds
Weak grip strength	Stratified by gender and body mass index (BMI) quartiles: <i>Men; cut-off for grip strength</i> BMI ≤ 24 ; ≤ 29 kg BMI 24.1–26; ≤ 30 kg BMI 26.1–28; ≤ 30 kg BMI > 28 ; ≤ 32 kg <i>Women; cut-off for grip strength</i> BMI ≤ 23 ; ≤ 17 kg BMI 23.1–26; ≤ 17.3 kg BMI 26.1–29; ≤ 18 kg BMI > 29 ; ≤ 21 kg

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