Original Research Open Access

Relationship between Frailty Status and Polypharmacy and Co-morbidities Among Elderly Patients Attending Outpatient Clinics at Ain Shams University Hospitals

Hagar M. Gasser[1], Sherine M. H. Elbanouby[1], Rania M. Abou-Hashem[1], Manar M. A. Maamoun[1]
[1]*Geriatrics and Gerontology Department, Faculty of Medicine, Ain Shams University*

Abstract

Background: The elderly population is a growing heterogeneous group with diverse needs and functional status that falls under different frailty stages. Hence, it is used as a risk stratification concept to be implemented in preventative and interventional strategies. It is related to the increasing number of drugs and morbidities in the geriatrics population

Aim: to study the prevalence of frailty and pre-frailty and its relation to the number of comorbidities and medications received among elderly patients attending the outpatient clinics of Ain Shams University Hospital

Methods: A cross-sectional study including 104 elderly from the geriatrics outpatient clinic of Ain Shams University hospitals. Frailty status was determined using the clinical frailty scale during their visit to the clinic. Then detect the prevalence of comorbidities and polypharmacy among the different states of frailty.

Results: The present study showed that by using the clinical frailty scale 48% are frail, 22.1% are pre-frail and 29.9% are not frail. It was also found that the number of comorbidities and medications is related to frailty in an increasing fashion.

Conclusion: Frailty and pre-frailty are prevalent in elderly. It is strongly associated with number of medications using the clinical frail scale. High numbers of comorbidities are correlated with the frail status.

Keywords: Frailty, pre-frailty, the clinical frail scale, ADL, IADL, comorbidities, polypharmacy.

Background

Frailty is largely prevailing geriatric syndrome, with preliminary evidence as regards the pathophysiology and the clinical phenotype of the syndrome, requiring early identification and taking specific measures to meet its needs. [(1)].

It is a term that describes the decline in physiological reserve associated with the aging process, rendering the frail individual more vulnerable to morbidities and mortalities and less able to withstand outside stressors carrying an increased risk for adverse health outcomes as disability and hospitalization with depleted homeostatic reserve [(2)]

Several factors play a role in frailty status including lifestyle, social, psychological and health problems. Chronic inflammation and chronic illnesses have taken their toll on determining the frailty status[(3)].

Frailty and multiple comorbidities were used interchangeably to identify vulnerable elderly. However, growing research done by geriatricians made it clear that although interrelated, the two terms are separate entities with unique challenges requiring different approaches [(4)].

Polypharmacy is another domain that is widely studied in the frail population mostly because of the intertwined impact they both have on each other. Moreover, further studies showed that the possibility of being frail or even pre-frail increases with every added medication [(5)].

AIM OF THE STUDY

The aim of our study was to identify the prevalence of frailty and pre-frailty in the elderly subjects attending the outpatient clinics of Ain Shams University Hospitals and determine the relationship between frail state and the number of comorbidities and the number of drugs.

MATERIALS AND METHODS

A cross sectional study done on 104 subjects chosen from elderly attending the outpatient clinics of Ain Shams university Hospital. All participants were

interviewed after giving an informed consent. The participants underwent the comprehensive geriatrics assessment including; Demographic data, past medical history and reviewing the medications received.

The subject had undergone cognitive function assessment using the Mini-Mental State Examination (MMSE) [6], Arabic version [7]. Assessment of physical function using activities of daily living (ADL) and instrumental activities of daily living (IADL)[8] was also done.

Then, the frailty state was assessed using the clinical frailty scale during their visit to the clinic. Subjects were categorized into 9 groups from 1 (Very fit) to 9 (terminally ill) [9]. For the purpose of the study, the CFS was divided into three categories: non-frail, vulnerable, and frail [10]

Next step, participants were categorized into two groups regarding the number of medications received into two groups First group receives less than 5 drugs while the second group receives 5 or more drugs based on defining polypharmacy as using 5 or more medications as used by several studies among which is ***Gnjidic et al. (2012)*** [11]**.. *Gutiérrez et al.(2018)*** [12]**.** mentioned that the definitions of polypharmacy varied between studies, from more than three to more than six medications, but the most repeated definition is the use of five or more drugs as mentioned by ***Masnoon et al. (2017)*** [13]**.** citing 1156 articles in a systemic review. Subjects were asked namely about receiving statins, anticholinergics, sedatives or corticosteroids. Statins were under the scope of several studies analyzing their benefit in reducing the rates of all-cause mortality by 22% and coronary death by 30%. [14]**.** This overall benefit was found to be less prominent in frail elderly as many of the secondary prevention trials evaluated the outcomes over several years therefore not generalizable to the frail elderly. [15]**.** Statins were also found to contribute indirectly to frailty as they cause problematic side effects including myopathies that may lead to deconditioning**.** [16]**.** On the other hand, **Lacroix et al., 2008** [17]**.** stated that most epidemiological studies suggest that statins are not associated with an increase in the risk of developing frailty.

A cross sectional study examined the association between medicine use and frailty in community-dwelling elderly found that showed that older people who were identified as frail were more likely to use analgesics among other inappropriate medicines measured by the drug burden index, which includes sedative and anticholinergic medicines [18]**.** As regards the number of comorbidities, patients are divided in three groups. First groups are those who have no diseases, second group includes individuals with 1-3 diseases and the third group are individuals with more than 3 diseases [19]**.**

Among the co-morbidities involved in our study are respiratory and cardiac diseases specifically heart failure, coronary artery disease, COPD and interstitial lung diseases. Hypertension, diabetes mellitus, hearing and visual impairment, chronic liver and renal disease hypothyroid and hyperthyroidism were also included. This group of co-morbidities was chosen based on several studies examining the most strongly frailty-associated diseases. Hypertension, congestive heart failure and depression were among the most common chronic diseases prevalent in frail elderly [20]**.**

Inclusion criteria were: Elderly above 60 years old attending outpatient clinic. We excluded patients with cognitive impairment using the Mini Mental state examination (scoring less than 24 adjusted for age and education). Subjects who were unwilling to participate in the study and acutely ill patients requiring urgent management were also excluded from our study.

Data obtained is analyzed to identify the relationship between polypharmacy and frailty, and whether the number of morbidities is related to the subjects' frailty status.

Statistical analysis

The collected data were coded, tabulated, and statistically analyzed using IBM SPSS statistics (Statistical Package for Social Sciences) software version 22.0. The level of significance was taken at P value < 0.05 is significant, otherwise is non-significant. Quantitative date. e.g., age, weight, will be presented as mean and standard deviation. Independent t-test will be used to compare quantitative data between the two groups. Qualitative data, e.g., frailty, obesity, will be presented as count and proportion. Chi-squared test will be used to compare the proportions between the two groups.

Results

Table [1] shows that study participants' age ranged between 60 to 90 years old 26.9% of the population are smokers and 29.8% illiterates. Concerning the residence, most of the cases (84.6%) live with their families. Regarding the marital status, more than half of the cases (52.9%) are married. It also shows that the prevalence of frailty was 48% in the outpatient clinics while 22.1% where vulnerable. Last column in the same table showed that 49.1% of our subjects had more than 3 illnesses and only 3.8% did not have any illnesses, while three quarters of them receive less than 5 medications. A highly statistically significant relationship between Frailty and the number of comorbidities and polypharmacy was shown by clinical frailty scale as presented in **table [2] and [3].** 74.2% of the non-frail adults had 1-3 comorbidities, while 74% of the frail adults had more than 3 comorbidities. Regarding the number of medications, all the fit participants received less than 5 medications. This percent decreases as we move across the table to higher frailty levels; nearly fifth of the vulnerable adults receive 5 or more medications and the percentage goes up to 42% among the frail ones.

Table (1): Characteristics of the Studied Population:

		No.	%
Age	60-70 years	45	43.3%
	71-80 years	38	36.5%
	81-90 years	21	20.2%
Sex	Male	47	45.2%
	Female	57	54.8%
Occupation	Retired	30	28.8%
	Manual Labor	12	11.5%
	Office job	15	14.4%
	Housewife	47	45.2%
Education	Illiterate	31	29.8%
	can read and write	24	23.1%
	<6 years	10	9.6%
	>6 years	16	15.4%
	highly educated	23	22.1%
Residence	Lives alone	13	12.5%
	lives with family	88	84.6%
	Institutionalised	3	2.9%
Marital	Married	55	52.9%
	Widowed	41	39.4%
	Divorced	6	5.8%
	Single	2	1.9%
Smoker	Non-smoker	62	59.6%
	Smoker	28	26.9%
	Ex-smoker	14	13.5%
Clinical Frailty Scale	Non – frail	31	29.9%
	Pre-frail	23	22.1%
	Frail	50	48.0 %
No. of co-morbidities	0	4	3.8%
	1-3	49	47.1%
	>3	51	49.1%
Medications	<5	78	75.0%
	≥5	26	25.0%

Table (2): Relationship between Frailty by clinical frailty scale and the number of comorbidities:

		Clinical Frailty Scale						p-value	Sig.
		Non-frail		Pre-frail		Frail			
		No.	%	No.	%	No.	%		
No. of co morbidities	0	2	50%	1	25 %	1	25%	<0.001	HS
	1-3	23	46.9%	14	28.5%	12	24.4%		
	>3	6	11.7%	8	15.6%	37	72.5%		

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS)

Figure 1: Correlation between frailty and number of comorbidities using the CFS:

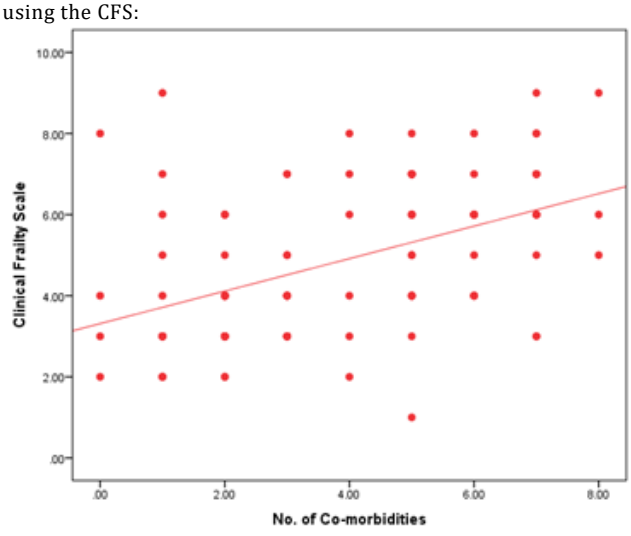

Figure (2) Correlation between frailty and number of medications using the CFS

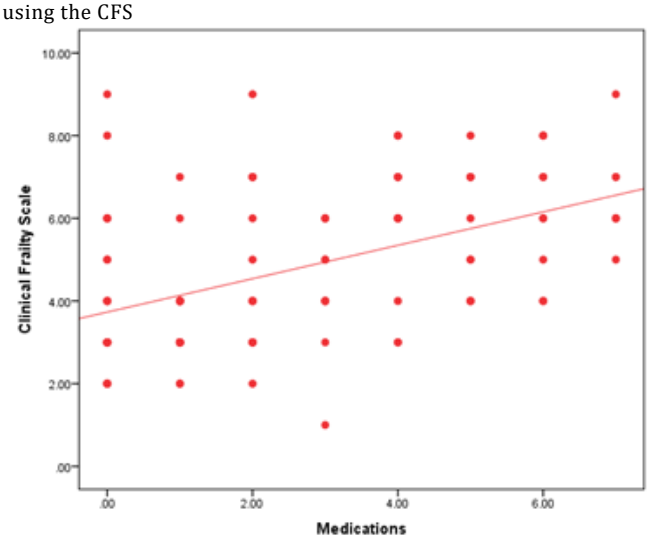

Table (3): Relationship between frailty and different medical disorders using the Clinical Frailty Scale:

		Clinical Frailty Scale						P-value	Sig.
		Not frail		Pre frail		Frail			
		No.	%	No.	%	No.	%		
DM	Yes	8	17%	27	57.4%	12	25.5%	0.035	S
	No	23	40.3%	23	40.3%	11	19.2%		
HTN	Yes	11	22.4%	24	48.9%	14	28.5%	0.179	NS
	No	20	36.3%	26	47.2%	9	16.3%		
Cardiovascular disease	Yes	2	5.8%	20	58.8%	12	35.2%	0.001	HS
	No	29	41.4%	30	42.8%	11	15.7%		
COPD	Yes	9	36.0%	13	52.0%	3	12.0%	0.359	NS
	No	22	27.8%	37	46.8%	20	25.3%		
BPH	Yes	7	26.9%	15	57.6%	4	15.4%	0.479	NS
	No	24	30.7%	35	44.8%	19	24.3%		
CLD	Yes	11	42.3%	11	42.3%	4	15.4%	0.25*1	NS
	No	20	25.6%	39	50.0%	19	24.3%		
CKD	Yes	8	20.0%	21	52.5%	11	27.5%	0.200	NS
	No	23	35.9%	29	45.3%	12	18.7%		

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS)
*:Chi-square test

Table (4): Relationship between frailty by clinical frailty scale and number of medications

		Clinical Frailty Scale						p-value	Sig.
		Non-frail		Pre-frail		Frail			
		No.	%	No.	%	No.	%		
Medication	<5	31	39.7%	18	23%	29	37.3%	<0.001	HS
	≥5	0	0.0%	5	19.2%	21	80.8%		

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS)

Table (5): Relationship between specific medications and frailty status using the Clinical Frailty Scale :

		Clinical Frailty Scale						P-value	Sig.
		No frail		Prefrail		Frail			
		No.	%	No.	%	No.	%		
Corticosteroids	Yes	3	60%	2	40%	0	0.0%	0.242	NS
	No	28	28.2%	48	48.6%	23	23.2%		
ACEI	Yes	15	60%	10	40.0%	0	0.0%	0.000	HS
	No	16	20.2%	40	50.6%	23	29.1%		
Statins	Yes	14	73.6%	5	26.4%	0	0.0%	0.000	HS
	No	16	19%	45	53.5%	23	27.3%		

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS)
*:Chi-square test

Table (6): Multi variate logistic regression analysis for medications use and incident of frailty using of Clinical Frailty scale:

	B	S.E.	P-value	Odds ratio (OR)	95% C.I. for OR	
					Lower	Upper
ACEI	-1.360	0.626	0.030	0.257	0.075	0.875
Statins	-2.425	0.712	0.001	0.088	0.022	0.357

Discussion

Frailty is an important and a highly prevalent health problem in older adults that has a negative impact on health related outcomes. The importance of studying frailty comes from the fact that its merely an association with aging and not an inevitable process, hence, it can be prevented or treated ***(Ahmed et al., 2007)*** [(21)]**.**

The British Geriatrics Society recommends that any encounter between an elderly and healthcare services should include an assessment of his frailty status.

The primary purpose of this study was to study the prevalence of frailty and pre-frailty in outpatient clinics and its relationship to the number of comorbidities and the number of medications using the clinical frail scale.

The present study showed that by using the clinical frail scale, the prevalence of frailty and pre-frailty was 48% and 22.1% respectively.

Previous studies reported slight differences of prevalence rates of frailty among elderly people. This heterogeneity can be explained by differences in participants' characteristics (e.g., sex, mean age, frailty status, co-morbidities, etc.), study setting (community, care homes, etc.) and methodological differences.

However, a systematic review including 56 studies showed that the prevalence of frailty varied from 3.9% to 51.4% and prevalence of pre-frailty ranged from 13.4% to 71.6% [22)]**.**

The prevalence of frailty varied from 3.9% in China (Fried phenotype with five criteria—weakness and slowness assessed using objective tests) to 51.4% in Cuba (Cuban frailty criteria) and prevalence of pre-frailty ranged from 13.4% in Tanzania (Brief Frailty Instrument for Tanzania, B-FIT) to 71.6% in Brazil (Fried phenotype with five criteria—weakness and slowness measured objectively) for the studies with minimum recruitment age 60, 65 and 70 years.

Frailty was found to be linked to various risk factors among which is the number of comorbidities. Congestive heart failure and depression are amongst the most closely associated morbidities, although no specific disease is confirmed to be more strongly associated than the others [(23)]**.**

Nearly half of our subjects (49.1%) had 3 or more co-morbidities. By the clinical frail scale, our study found that half of those with no comorbidities were non frail, while 25% were frail.

And the percentage of frail elderly increases as the number of comorbidities increase, where frail elderly form 72.5% of those having more than 3 comorbidities . With 95% confidence, there is a highly significant relationship between the number of co-morbidities and frailty.

This was in agreement with ***Wong et al. (2010)*** [(24)] that found that 81% of the frail subjects in his study had comorbidities that he defined as the presence of two or more of the following chronic diseases: hypertension, cardiac problems, peripheral circulatory problems, respiratory problems, arthritis, cancer and diabetes. Also the cardiovascular health study stated that 67.7% of frail adults had multi-morbidity which they defined as two or more diseases [(25)]**.**

Our study also found that single specific disease were more related to frailty than others; diabetes was found to be significantly related to frailty state as 82.9% of the diabetics were either frail or pre-frail (percentages were 25.5% and 57.4% respectively) and only 17% were non frail.

This was in agreement with the prospective cohort study conducted on 1750 elderly diabetes showing an increased risk of frailty (odds ratio [OR] 2.18, 95% confidence interval [CI] 1.42–3.37). [(26)]**.**

Similarly cardiovascular diseases showed a highly significant relationship, were 35.2% of the diseased were frail and only 5.8% non-frail. Results from a study on 1432 elderly resembled ours where in the age and sex adjusted models, subjects with cardiovascular disease were more likely to be frail than subjects without CVD ,odds ratios varied from 1.92 to 3.50 and reached statistically significance in the analyses with any CVD**.** [(27)]**.**

Hypertension, chest diseases, liver and kidney diseases were not found to have a relationship with frailty in our study this was against what ***Aprahamian et al., 2017*** [(28)]**.** concluded in their paper where hypertension was an associated risk factor for frailty and was more prevalent

among frail older adults; prevalence of hypertension was 67.3% in the total sample and was higher among the frail (n = 78) (P < .001; Table 2) and prefrail (n =235) (P < .001) groups. This could be attributed in part to the fact that comorbidities were self reported by the participants and not from medical records.

As regards polypharmacy, 80% of the subjects receiving more than 5 medications were found to be frail using the clinical frailty scale, with all the individuals that are non-frail taking less than 5 medications.

However, the percentage of those who take more than 5 medications increases as the severity of frailty increases. Surveying the literature, several studies show that the mean drug consumption by frail patients is higher than that of robust ones ***(Ballew et al., 2017)*** [(29)]**.** Although in ***Perera et al. (2009)*** [(30)]**.** the difference between the mean drug consumption by frail and non-frail was not statistically significant for a group of hospitalized patients aged ≥ 70 years with atrial fibrillation.

Gnjidic et al. (2012) [(31)]**.** established that the optimal discriminating number of concomitant medications associated with the presence of frailty was 6.5.

Other studies revealed that the prevalence of frailty was higher among patients with polypharmacy or hyper-polypharmacy (≥10 drugs) [(32)]**.**

The participants were asked specifically about drugs that were suggested by the literature to be related to frailty and its progression, namely angiotensin converting enzyme inhibitor, statins and corticosteroids whatever the duration and the dose were. It's worth noting that only 5 of the 104 participants received steroids, 25 receiving ACE-I and 19 for statins.

It was found that both ACE-I and statins were highly statistically related to frailty as 60% of those on ACE-I medications were non frail and no one was frail, also no one of the participants compliant on statins were frail and up to 73.6% are not frail. By using the logistic regression analysis, both were shown to decrease risk of frail state. Odds ratio in the range of 0.07 to 0.8 for ACE-I and 0.02 to 0.3 for statins (multivariate adjusted). By reviewing the literature it was found that current statin use had no association with incident frailty (odds ratio [OR] = 1.00; 95% confidence interval [CI], 0.85–1.16). [(33)]**.**

But on the other hand and in agreement with our results, a cohort with 8 years follow up concluded that the use of ACEI was associated with a lower risk of frailty (RR 0.72; 95% CI 0.53–0.99). [(34)]**.** The use of corticosteroids showed no relationship with frailty state using the CFS in our study.

However, polypharmacy and multi-morbidities can be recognized as major contributors to the frail state. Frailty is correlated positively with the number of co morbidities and number of medications received as seen in figure (1) and figure (2) respectively.

Polypharmacy should be assessed in frail subject with medications review on every encounter. Proper control of comorbidities is a cornerstone in preventing and arresting the progress of frailty, and can lead to decrease in the number of medications received.

CONCLUSION

Frailty and pre-frailty state is prevalent in elderly attending the outpatient clinics. It is strongly associated with number of comorbidities and polypharmacy.

Ethical considerations

Informed consent was taken from every elderly participating in this study. The study methodology was reviewed and approved by the Research Review Board of the Geriatrics and Gerontology Department, Faculty of Medicine, Ain Shams University.

Disclosure Statement

There is no conflict of interest.

References

1. Chen X, Mao G, & Leng SX (2014): Frailty syndrome: an overview. Clinical interventions in aging, 9: 433-41.

2. Xue QL (2011): The frailty syndrome: definition and natural history. Clinics in geriatric medicine, 27(1): 1-15.

3. Maggio M, Guralnik JM, Longo DL, Ferrucci L (2006): Interleukin-6 in aging and chronic disease: a magnificent pathway. J Gerontol A Biol Sci Med Sci., 61(6): 575-84.

4. Fried LP, Ferrucci L, Darer J, Jeff D, Gerard A (2004): Untangling the Concepts of Disability, Frailty, and Comorbidity: Implications for Improved Targeting and Care, The Journals of Gerontology: Series A, 59(3): 255–263.

5. Herr M, Robine JM, Pinot J, Arvieu JJ, Ankri J (2015): Polypharmacy and frailty: prevalence, relationship, and impact on mortality in a French sample of 2350 old people. Pharmacoepidemiol Drug Saf, 24: 637-46.

6. Folstein MF, Folstein SE, McHugh PR (1975). "Mini-mental status". A practical method for grading the cognitive state of patients for the clinician. Journal of Psychiatric Research. 12 (3): 189–98

7. El-Okl M, El Banouby M and El Etrebi L (2002): A Prevalence of Alzheimer dementia and other causes of dementia in Egyptian elderly. MD Thesis, Faculty of Medicine, Ain Shams University.

8. Lawton MP, Brody EM (1969): Assessment of older people: Self-maintaining and instrumental activities of daily living. The Gerontologist; 9(3): 179-186.

9. Morley JE, Malmstrom TK and Miller DK (2012): A Simple frailty questionnaire (FRAIL) predicts outcomes in middle aged African Americans J Nutr Health Aging; 16(7): 601–608.

10. Juma S, Taabazuing MM and Montero-Odasso M (2016): Clinical Frailty Scale in an Acute Medicine Unit: a Simple Tool That Predicts Length of Stay. Can Geriatr J; 19(2):34-9.

11. Gnjidic D, Hilmer SN, Blyth FM, Naganathan V, Waite L, Seibel MJ, McLachlan AJ, Cumming RG, Handelsman DJ, Le Couteur DG (2012): Polypharmacy cutoff and outcomes: five or more medicines were used to identify community-dwelling older men at risk of different adverse outcomes. J Clin Epidemiol, 65: 989-95.

12. Gutiérrez V, Marta I, Mikel C, Matteo C, Alvaro I, Marco V (2018): The relationship between Frailty and Polypharmacy in older people: a Systematic Review. British journal of clinical pharmacology; 84(7):1432-44.

13. Masnoon N, Shakib S, Kalisch-Ellett L & Caughey GE (2017): What is polypharmacy? A systematic review of definitions. BMC Geriatrics, 17(1).

14. Afilalo J, Duque G, Steele R, Jukema JW, de Craen AJ, Eisenberg MJ (2008) Statins for secondary prevention in elderly patients: a hierarchical bayesian meta-analysis. J Am Coll Cardiol., 51:37–45.

15. Mallery L, Moorhouse P, McLea Veysey P, Allen M, Fleming I (2016) Frail elderly patients do not need lipid-lowering drugs. Cleve Clin J Med; 83:131–142.

16. Curfman G.(2017) Risks of Statin Therapy in Older Adults. JAMA Intern Med.;177(7):966.

17. LaCroix, Shelly L. Gray, Aaron Aragaki, Barbara B. Cochrane, Anne B. Newman, Charles L. Kooperberg, Henry Black, J. David Curb, Philip Greenland, Nancy F. Woods, Statin Use and Incident Frailty in Women Aged 65 Years or Older: Prospective Findings From the Women's Health Initiative Observational Study, The Journals of Gerontology: Series A, Volume 63, Issue 4, April 2008, Pages 369–375.

18. Koponen MH, Bell JS, Karttunen N, Nykänen I, Desplenter FM, Hartikainen S.(2013) Analgesic use and frailty among community- dwelling older people. Drugs Aging; 30(2): 129–36

19. Karen BR, Christopher LS, Jin H, Brian B, Rita RK, Ravi V, Qian-Li X, Jeremy DW, Judith DK. A Nationally Representative Profile in the United States, The Journals of Gerontology: Series A, 2015; 70(11): 1427–1434.

21. Ahmed, N., Mandel, R., & Fain, M. J. (2007). Frailty: An Emerging Geriatric Syndrome. The American Journal of Medicine, 120(9), 748–753.

22. Siriwardhana DD, Hardoon S, Rait G, Weerasinghe MC & Walters KR (2018): 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, 8(3): e018195.

23. Weiss CO (2011): Frailty and Chronic Diseases in Older Adults. Clinics in Geriatric Medicine, 27(1), pp. 39-52.

24. Wong CH, Weiss D, Sourial N, Karunananthan S, Quail J, Wolfson C, Bergman H (2009): Frailty and its association with disability and comorbidity in a community-dwelling sample of seniors in Montreal: A cross-sectional study. Aging clinical and experimental research. 22: 54-62.

25. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G, McBurnie MA. Frailty in Older Adults: Evidence for a Phenotype, The Journals of Gerontology, Series A, 2001; 56(3): 146–157.

26. García-Esquinas, E., Graciani, A., Guallar-Castillón, P., López-García, E., Rodríguez-Mañas, L., & Rodríguez-Artalejo, F. (2015). Diabetes and Risk of Frailty and Its Potential Mechanisms: A Prospective Cohort Study of Older Adults. Journal of the American Medical Directors Association, 16(9), 748–754.

27.Kleipool, E. E., Hoogendijk, E. O., Trappenburg, M. C., Handoko, M. L., Huisman, M., Peters, M. J., & Muller, M. (2018). Frailty in Older Adults with Cardiovascular Disease: Cause, Effect or Both? Aging and Disease, 9(3), 489.

28.Aprahamian, I, Sassaki, E, dos Santos, MF.(2018). Hypertension and frailty in older adults. J Clin Hypertens, 20: 186– 192.

29. Ballew SH, Chen Y, Daya NR, Godino JG, Windham BG, McAdams-DeMarco M, Coresh J, Selvin E, Grams ME (2017): Frailty, Kidney Function, and Polypharmacy: The Atherosclerosis Risk in Communities (ARIC) Study. Am J Kidney Dis., 69: 228-36.

30. Perera V, Bajorek BV, Matthews S, Hilmer SN (2009): The impact of frailty on the utilization of antithrombotic therapy in older patients with atrial fibrillation. Age Ageing, 38: 156-62.

31.Gnjidic D, Hilmer SN, Blyth FM, Naganathan V, Cumming RG, Handelsman DJ, McLachlan AJ, Abernethy DR, Banks E, Le Couteur DG (2012): High-risk prescribing and incidence of frailty among older community-dwelling men. Clin Pharmacol Ther; 91: 521-8.

32.Gnjidic D, Hilmer SN, Blyth FM, Naganathan V, Waite L, Seibel MJ, McLachlan AJ, Cumming RG, Handelsman DJ, Le Couteur DG (2012): Polypharmacy cutoff and outcomes: five or more medicines were used to identify community-dwelling older men at risk of different adverse outcomes. J Clin Epidemiol, 65: 989-95.

33. Lacroix, A. Z., Gray, S. L., Aragaki, A., Cochrane, B. B., Newman, A. B., Kooperberg, C. L., ... Woods, N. F. (2008). Statin Use and Incident Frailty in Women Aged 65 Years or Older: Prospective Findings From the Womens Health Initiative Observational Study. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences, 63(4), 369–375.

34. Veronese, N., Stubbs, B., Smith, L., Maggi, S., Jackson, S. E., Soysal, P., Koyanagi, A. (2019). Angiotensin-Converting Enzyme Inhibitor Use and Incident Frailty: A Longitudinal Cohort Study. Drugs & Aging, 36(4), 387–393.