Frailty in elderly patients with acute myocardial infarction

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Abstract
In recent years, there has been increasing interest in the frailty as a prognostic factor of acute myocardial infarction in elderly patients. Frailty is an important prognostic marker of frequent complications, readmission to hospital, high hospital mortality and major cardiovascular events in elderly patients with acute myocardial infarction. This category of persons is often not allowed to undergo invasive interventions and are often excluded from the recommended treatment, and they tolerate cardiac surgery worse, recovery from illness is slower, functionality decreases, then disability and death develop.

The present review aims to investigate the impact of frailty on management of elderly patients with acute myocardial infarction (AMI). To analyze the literature, we searched for information on this issue in PubMed / MEDLINE, PMC, Web of Science, Scopus, The Cochrane Library. The search depth was 15 years: from 2006 to 2021.

One of the important factors in improving clinical outcomes, improving the quality of life in elderly patients with acute myocardial infarction is the early detection of frailty. Frailty assessment is a valuable tool for risk stratification that can be helpful to clinicians in deciding the optimal pathway for management and treatment strategies. Risk prediction is also important for deciding secondary prevention and cardiac rehabilitation measures in the elderly with acute myocardial infarction.

Keywords: acute myocardial infarction, advanced age, frailty, prognosis, risk assessment.

Introduction
Life expectancy of population is increasing globally. According to the report by the United Nations, the share of the population aged 60 years or over is expected to rise from 617 million persons in 2015 to 2.1 billion by 2050 with the highest proportion of elderly persons in Asia [1].

Older individuals comprise a diverse cohort of population. Management of this group of patients must be tailored according to biological age, as patients of the same chronological age might differ in terms of functional status and living conditions. Cohort of aged individuals should be classified into three subgroups: robust, pre-frail (pre-asthenia) and frail (senile asthenia syndrome) [2].

Senile asthenia syndrome or frailty is a state of increased vulnerability to numerous factors resulting from aging-associated decline in function across multiple body systems. This condition leads to high rates of disablement, morbidity, and unfavourable prognoses. However, early detection of frailty allows for regression of this condition and better management of this group of patients [3].

Frailty is a complex clinical syndrome of increased vulnerability to stress factors, caused by multi-systemic functional decline. This in turn results in a mismatch between biological and chronological ages. Patients with low functional status and physiological reserve are at a higher risk of homeostatic imbalance when exposed to a stress factor [4]. Stress factors are classified into two major categories: acute or chronic diseases (acute myocardial infarction) and iatrogenic factors (surgical and medical treatment, interventions, hospitalization).
Pathophysiology of frailty

It is generally accepted that ageing is a result of lifelong accumulation of molecular and cellular damage caused by multiple mechanisms (genetic, behavioural, environmental factors, chronic diseases). A certain amount of cellular damage crucial for deterioration of organ function remains unclear. Most body systems make up a physiological reserve that is necessary to compensate age-related changes. Loss of physiologic reserve in these organs leads to frailty which is characterized by higher vulnerability to inadequate rebalancing of homeostasis after stress (acute illness, trauma, changes in treatment, surgery), increasing the risk of unfavourable outcomes such as falls, delirium, loss of functional capacity, disability. These common features of frailty cause higher rates of hospitalization and prompt further deterioration [8,9] (Figure 1).

Frailty is a syndrome of multisystemic dysregulation. Marked inflammation is observed as a reaction of immune system. Pathogenetic mechanisms of frailty include elevation of white blood cells count and levels of inflammatory cytokines IL-6 and C-reactive protein, this has a detrimental effect on body systems. Hyperinflammation plays the key role in pathogenesis of frailty acting directly or through other interim pathophysiological processes.

Yao Xu et al. provided an overview of current understanding of immunological alterations in frail patients describing them as a state of increased inflammation and compromised innate and adaptive components of immune system -immunosenescence. This leads to an increased morbidity and mortality rates in aged patients [10].

Ageing is associated with progressive modifications in T follicular helper cell (TFH) phenotype and function. Other subset of cells namely T-follicular regulatory cells exerts opposing roles to TFH cells in regulating immunity (TFH/T FR cell ratio). Imbalance in T FH/T FR cell ratio is an important component of frailty. Recent studies suggest that dysfunctional T FH play an essential role in the development of cardiovascular, oncological, autoimmune disorders. It is an all-encompassing process that predisposes to unfavourable reactions to vaccination and high infectious morbidity [11].

Risk factors for frailty

To date, numerous studies worldwide are focused on healthy ageing which is achieved by an adequate function of nervous, cardiovascular, and musculoskeletal systems. Lack of physical activity increases risks of developing chronic diseases, geriatric syndromes, and premature mortality [12,13].

Nutrition is another key component of healthy ageing. Lack of protein and overall malnutrition leads to sarcopenia, the loss of muscle mass and function. Poor functional status of musculoskeletal system can potentially lead to permanent disability and premature mortality [14]. The systematic review indicates the importance of adequate nutrition as balanced diet with sufficient intake of micronutrients and macronutrients may delay unfavourable outcomes of frailty [15] and frailty itself in elderly population.

Research suggests that low vitamin D levels correlate with an increased risk of developing frailty and sarcopenia. 25 hydroxy vitamin D deficiency in aged patients leads to low bone mineral density, higher rates of infectious diseases and consequently, frailty [16]. 80-90% of elderly individuals have vitamin D deficiency [17,18].
Polypharmacy (simultaneous administration of multiple medications) is another factor that may increase the risk of developing frailty. M. Gutierrez-Valencia et al. have identified the association between frailty and polypharmacy in aged patients (≥65 years old) in 21 of total 25 reviewed studies. According to the conclusion of the review, drug dose reduction and decreasing the number of administered medications could be a cautious strategy to prevent frailty in patients of advanced age [19]. In meta-analysis of 37 studies Palmer et al. have identified polypharmacy in 59% of frail patients [20]. M. Herr et al. [21] identified a 17% incidence of frailty among studied population, with polypharmacy detected in 54%, among these 14% of patients received more than 10 medications daily. The study has shown direct correlation between frailty and polypharmacy and increased mortality risks in the following years (RR=6.30, 95% CI 3.09-12.84).

Elderly patients with pre-frailty and frailty should be evaluated for feeling of exhaustion and its causes. Longitudinal Aging Study of Amsterdam (LASA) and Invecchiare in Chianti (InCHIANTI) have identified an exhaustion as the first symptom of frailty [22].

Epidemiology of frailty

According to studies, the prevalence of frailty varies widely and depends on the age, gender, race, physical activity, country of origin, diagnostic criteria, and other factors [23].

Systematic review with over 61 thousand enrolled patients has indicated the prevalence of frailty and pre-frailty as 10.7% and 41.6% respectively. The prevalence of frailty among patients living in nursing homes was 52.3% [24].

Siriwardhana DD et al. evaluated the prevalence of frailty among patients in low-, middle- and high-income countries. Levels of income were evaluated according to World bank classification. The results showed that general prevalence of pre-frailty in low-income countries was 49.3% (95% CI from 46.4% to 52.2%, I² = 97.5%), ranging from 13.4% in Tanzania and 40.7%-71.6% in Brazil. The mean prevalence of frailty was 17.4% (95% CI from 14.4% to 20.7%, I² = 99.2%), results ranged between 3.9% in China, 26% in India and 51.4% in Cuba. The prevalence of frailty peaked after 75 years of age with higher rates in women. Pre-frailty and frailty rates were higher in middle-income countries compared to high-income countries (Z = -8.86, P <0.001) and (Z = -17.14, P <0.001) respectively [25].

Asian countries with higher income showed lower rates of frailty (Japan, Singapore, Taiwan) compared to middle-income countries [26-28].

Multicenter study has estimated the prevalence of pre-frailty and frailty in Indonesia, results were 66.25% and 18.7% respectively. Main factors of frailty among Indonesian older adults were functional dependency (OR 5.97, 95% CI 4.04–8.80), malnutrition and depression (OR 2.54, 95% CI 1.56–4.12) and (OR 2.56, 95% CI 1.68–3.90) respectively. Falls (OR 1.77, 95% CI 1.16–2.72) and hospital admissions during the period of 12 months (OR 1.46, 95% CI 0.97–2.20) were also associated with frailty. Corelation between frailty and polypharmacy was also identified (OR 2.42, 95% CI 1.50–3.91) [29].

Shinkai S. et al. have identified epidemiologic properties of frailty in 2 decade long prospective study of elderly in Japan. The prevalence of frailty among men and women were 24.3% and 32.4% respectively. Higher incidence of frailty and its progression is observed in adults aged ≥80 years [30].

The prevalence of frailty is higher in individuals with low social and economic status and low level of education [31,32].

Clinical hallmarks of frailty

Higher probability and higher risks of developing frailty in patients of advanced age can be evaluated by several clinical symptoms. Unintentional weight loss over 5 kg in one year, muscle weakness, low physical activity, fatigue, urinary incontinence, falls, delirium, functional dependence, decline in cognitive functions, increased risk of infections are the major signs of frailty [33].

Frailty and COVID-19

At present, COVID-19 pandemic (SARS-CoV-2) has increased mortality in elderly patients according to international reports [34-36]. By August 23 2021, more than 216,3 million cases of COVID-19 and 4,5 million deaths were reported worldwide. 849 557 cases were reported in Kazakhstan, with 12 655 deaths [37]. Mortality from COVID-19 has a linear correlation with age [38].

In this setting age is not the only prognostic predictor. Perhaps frailty and high comorbidity rate cause vulnerability to unfavourable outcomes and mortality in this group of patients. Thus, numerous studies have stressed the role of frailty evaluation in patients with COVID-19.

European multicenter observational cohort study with 1564 enrolled patients by Jonathan Hewitt et al. has identified that among patients with COVID-19 with mean age of 74 years, frailty prevalence was 49.4% (5-8 according to CFS scale) and mortality was 27.2%. The analysis of study indicated a high mortality risk and prolonged hospitalization in frail elderly patients with COVID-19 (p<0.0001). Reported results are valuable for frailty estimation in combination with factors other than age, such as COVID-19 and other comorbidities [39].

According to a study with 3817 enrolled patients with COVID-19 an increase in reported clinical frailty scale score (CFS) by 1 point correlated with a 12% increase in mortality [40]. Similar results were reported in patients with COVID-19 hospitalized in Madrid, Spain [41]. In this study 30.71% of patients were classified as frail (including pre-frail patients). Comorbidities (cardiovascular diseases, kidney diseases, dementia), residential care homes dwelling, female sex category, advanced age were the predictors of high risk in frail patients. Frailty was a high mortality predictor in COVID-19 patients (RR: 1.39, 95% CI [1.07–1.81]. As it was outlined in other studies, delirium was identified as a common clinical manifestation of COVID-19 and is the main predictor of mortality in frail patients [42-44]. Mentioned studies have shown the association between COVID-19 and frailty, therefore frailty in combination with other comorbidities may indicate high risk of unfavourable outcomes and mortality in aged patients with COVID-19.

Infections cause biological damage and homeostasis imbalance which leads to progressive senescence and development of geriatric syndromes, forming vicious circle [45].

Identification of frailty may assist healthcare practitioners in distinguishing high-risk group of elderly patients requiring special attention and intervention to prevent unfavourable outcomes, improve quality of life and prognosis [46].

Frailty as a prognostic factor of acute myocardial infarction (AMI) in patients of advanced age

Advanced age is a major risk factor for unfavorable outcomes in AMI as this cohort of population has higher rates of comorbidities, functional changes, and low physiological reserve. However, there is a substantial heterogeneity in this
Stress factors, such as ACS, invasive manipulations and recently, the COVID-19 pandemic, put frail patients at higher risk and may potentially lead to unfavorable outcomes [48]. Frail patients with ACS frequently report complications, high hospital mortality rate, hospital readmissions. This cohort of patients are less likely to receive invasive manipulations, frequently have modified treatment based on their condition, have longer periods of recovery after cardiovascular surgeries [49-51].

Studies have shown the effect of frailty on short- and long-term outcomes after AMI. In systematic review and meta-analysis of 20 studies including 143 301 participants with mean age of 75 years authors concluded that among patients with AMI frailty was statistically associated with a twofold mortality risk compared with non-frail patients. Analysis also shows statistically higher risks of severe bleeding in frail patients compared with non-frail HR 1,34 (95% CI: 1,12–1,59, P = 0,001, I² = 4,7%). The prevalence of frailty in mentioned studies was 5,3%- 53,7% [52].

Uchmanowicz I et al. Identified that frailty occurred in 80% of patients after AMI, and has negative impact on physical, psychological, and social domains of life [53].

TRILOGY ACS trial included patients with non-ST segment elevation acute coronary syndrome. 25% of patients were frail. Frailty was associated with higher cardiovascular mortality [54]. According to CONCORDANCE registry frail patients with ACS had high in-hospital mortality and 6 month all-cause mortality rates (OR: 1,38, 95% CI: 1,05–1,83, p = 0,02) and (OR: 1,74, 95% CI: 1,37–2,22, compared with healthy :<0,001) respectively [55]. Systematic review and meta-analysis including 8,554 patients with ACS investigated corrected mortality odds for patients with STEMI (RR 6,51; 95% CI). and NSTEMI (relative risk 2,63; 95% confidence interval [1,51–4,60]). Higher risks of death were observed in pre-frail patients (corrected RR 1,41; 95% CI [1,19–1,66]) [56]. In a study by Kang et al. [57] 40% of total 352 patients were frail. Frailty in patients with ACS is a significant predictive factor of short- term treatment outcomes. The results of mentioned studies emphasize serious health issues in frail adults that should prompt timely evaluation of this condition.

Older individuals have lower food intake which leads to malnutrition. Malnutrition is major a risk factor for developing frailty that can be successfully modified [58]. Malnutrition is widely observed in frail patients with AMI undergoing PCI being a negative prognostic indicator of all-cause mortality. First major cohort study has shown the association between malnutrition and unfavorable outcomes in older patients undergoing PCI. Kaplan Meier analysis showed higher risk of all-cause mortality in malnourished patients [59].

In an observational study aged patients with slow gait speed more frequently sought medical assistance and had higher rates of hospitalization in 1-year period as well as higher mortality in 4-year period (32% with 9%) [60].

Older patients have a high rate of hospital readmission 30 days after hospitalization with AMI and subsequent discharge. Causes are partly associated with the impact of AMI and functional impairment which is frequently observed in frail patients [61]. John A. Dodson et al. studied data from prospective multicenter cohort trial SILVER-AMI. Results showed that in older patients during repeated readmission 30 days after AMI several functional impairments were reported (physical activity, visual function, weak grip strength, disability). The strongest factor that doubled risks of readmissions in patients with AMI was impaired mobility (OR for TUG 15-25 sec = 1,46, 95% CI 0,98-2,17; OR for TUG ≥25 sec = 1,86, 95% CI 1,32-2,61; OR for TUG, unable to finish = 1,49, 95% CI 1,01–2,19) [62].

Cognitive frailty, hearing and vision impairment result in issues with compliance in taking prescribed medications, injuries caused by falls, unintentional weight loss and higher susceptibility to infections. Mentioned functional impairments are associated with hospital readmissions as well.

European Society of Cardiology and American Heart Association underlined the importance of frailty assessment in management of elderly patients with AMI [63] as these efforts will have a major impact on preventive measures and treatment strategies. But to date there is no special tools for mortality risk estimation in frail patients with AMI. Number of other professional cardiac and geriatric associations emphasize the importance of risk stratification tools for aged patients as well [64].

**Frailty screening and assessment tools**

Aged frail patients experience more prominent exertion on homeostasis in case of AMI compared with healthy individuals. This in turn leads to marked functional disturbances in multiple body systems, increasing risks of hospitalization and death. Considering the increase in proportion of elderly patients with AMI, cardiologists will encounter frail patients with multiple comorbidities more frequently. There is no common opinion on validation of frailty assessment tools. Complex assessment of geriatric patients seems impossible in a routine clinical practice thus adequate adaptation of appropriate tools should be carried out according to particular settings.

Over 20 frailty assessment tools have been introduced [65], most of them focused on 5 phenotypes- slow gait speed, reduced physical activity, exhaustion, and weight loss. Currently, there are two major operational definitions of frailty: frailty phenotype proposed and validated by L.P. Fried et al. and the frailty index by K Rockwood et al. that deems the deficit accumulation as most important factor of frailty.

The definition of frailty phenotype by L.P.Fried at al. [66] is based on Cardiovascular Health Study including over 5 thousand participants, men and women aged 65 years and older. General prevalence of frailty according to the results was 7%, with higher rates in women (14,4%) as opposed to men (7,4%). This definition describes frailty as a decrease in physiological reserves and includes five criteria: unintentional weight loss in past 12 months, self-reported exhaustion, low physical activity, slow gait speed, weakness (grip strength according to dynamometry). The presence of three criteria out of five is sufficient to diagnose frailty. One established criterion out of five is considered pre-frailty. This definition is most reliable and cited.

Another operational definition of frailty is frailty index (FI), or accumulation of deficits across various domains established by K. Rockwood et al. based on Canadian Study of Health and Aging including 10 263 patients, with most patients aged between 75-84 years old. This definition describes the presence of comorbidities, geriatric syndromes and symptoms and includes a count of 70 items. Frailty index is estimated as a ratio of deficits present in given patient to total number of 70 deficits. The closer the result is to 1 the more severe is frailty [67].

The task force of the International Conference of Frailty and Sarcopenia Research (ICFSR) recommends the use of well-studied frailty phenotype by L.P.Fried et al [68].
Frailty assessment scales for patients with AMI

Numerous scales, modified questionnaires and tests have been introduced for the assessment of pre-fraility and frailty. Main scales suitable for frailty assessment in AMI patients are listed below.

Frailty assessment scales based on interviewing without objective assessment of physical performance

FRAIL scale

This assessment scale consists of five main domains: fatigue, resistance, ambulation, illness, and weight loss. When three or more of these deficits are present, a patient is classified as frail. Advantages of this scale are assessment of multiple domains. Disadvantages are time consuming assessment, lack of data on frail AMI patients, the absence of important laboratory parameters. Prognostic value in AMI: this scale is a predictive tool of 6-month mortality from all causes [69].

Frailty index (FI)

This scale is a 32-item tool based on evaluation of symptoms, signs, disability, illness, and laboratory parameters. The results higher than 0,25 are considered as identifying frailty. Advantages. This is a practical tool for rapid assessment of frailty. Disadvantages. The scale is subjective, lacks multidimensional approach and clinical and laboratory evaluation. Prognostic value in AMI: association with long term mortality [70].

Clinical frailty scale (CFS)

CFS is a 9-point scale, with 1 point considered as “very fit” and 9 points as “terminally ill”. Frailty is assessed with simple questions according to description of each of 9 levels. Advantages. This is practical tool for rapid assessment of frailty. Disadvantages: CFS is subjective, lacks multidimensional approach and clinical and laboratory evaluation. Prognostic value in AMI: this tool is a predictive tool for hospital mortality, 1-month mortality, and prolonged hospitalization [71].

Frailty assessment scales based on physical performance evaluation

Fried frailty criteria

This scale is based on 5 criteria: unintentional weight loss > 4,5 kg in less than a year, exhaustion, low physical activity, slow gait speed and grip strength (frailty is diagnosed in presence of 3 to 5 criteria). Advantages. High evidence level in the assessment of frailty, multidomain evaluation. Disadvantages. Introductory course in geriatrics is a prerequisite, time consuming scale. Lack of clinical and laboratory evaluation. Prognostic value in AMI: strong predictive value of mortality from myocardial infarction [72].

Frailty Instrument for Primary Care of the Survey of Health, Ageing and Retirement in Europe or SHARE-FI

SHARE-FI is a 6-point tool that evaluates fatigue, appetite, physical activity, ambulation, resistance and grip strength. Advantages. Multi domain rapid and practical assessment. Disadvantages. The absence of clinical and laboratory evaluation. Prognostic value in AMI: strong association with early complications and survival rates [73].

Edmonton frail scale (EFS)

This is a 17-point questionnaire consisting of questions related to nutrition, symptoms, mood, and physical performance with 0 points indication as “not frail” and 17 points as “severe frailty”.

Advantages. Multidimensional assessment of frailty. Disadvantages. Time-consuming process of assessment. Prognostic value in AMI: association with the duration of hospitalization, 1-year mortality and inadequate management [74].

Green score

This is a 12-point (evaluation of following domains: physical activity, serum albumin levels, gait speed, grip strength) scale. Advantages. Multidimensional assessment of frailty including laboratory studies. Disadvantages. This scale does not include comorbidity assessment. Prognostic value in AMI: association with all-cause mortality and recurrent myocardial infarction risks [75].

Assessment of physical performance

Grip strength

Grip strength measured using a hand-held dynamometer is a good indicator of upper limb global strength. Advantages. Allows for practical and rapid evaluation. Disadvantages. This is non multidimensional assessment. Absence of relevant clinical and laboratory evaluation. Prognostic value in AMI: predictive factor of cardiovascular mortality, all-cause mortality, and hospitalizations for heart failure [76].

Gait speed

The assessment of usual gait speed on several meters (most used distance is 5-10 meters). Gait speed is considered as “slow” in case if it is ≤ 0,8 meters per second. Advantages. This is practical and rapid assessment tool. Disadvantages. This is non multidimensional assessment. Absence of relevant clinical and laboratory evaluation. Prognostic value in AMI: predictive factor of 1-year mortality and hospital readmissions [77].

Short physical performance battery (SPPB)

SPPB is the functional assessment of lower extremities based on three tests: balance test, gait speed and chair stand. Results range between 0 (worst performance) and 12 (best performance). Physical performance is considered low if SPPB ≤ 9. Advantages. Multi-domain assessment of physical performance. Disadvantages. Geriatric educational course is a prerequisite. Absence of clinical and laboratory studies. Prognostic value in AMI: the usefulness of this tool is currently being studied [78].

Frailty assessment during an acute phase of acute coronary syndrome

Frailty assessment during an acute phase of ACS has it’s characteristic features. During the admission of patients with ACS frailty assessment may be carried out using practical and rapid scales based on interviewing the patient without the evaluation of physical performance. Most suitable scales in this setting are FRAIL scale and clinical frailty scale CFS.

Frailty evaluation after the acute phase of acute coronary syndrome

Accurate assessment of frailty with the analysis of physical performance in patients with ACS is possible to carry out 48
hours after admission. This allows for more precise evaluation of frailty and its prognosis. Most suitable scales in this setting are Green score, Freid frailty criteria, SHARE-FI, gait speed, Edmonton frail scale. Those scales have the strongest prognostic value. However, data on the most appropriate time period for frailty assessment during hospitalization is scarce [79].

Currently the frailty phenotype proposed and validated by L.P. Fried et al. and the frailty index by K.Rockwood et al. are the two most widely used tools for screening and assessment of frailty. Frailty index is the most appropriate tool for the evaluation of frailty after relevant interventions [80].

Campo et al. have compared seven tools of frailty assessment in patients with AMI. SPPB, EFS and Fried scale were the most precise in terms of correlation with 1-year all-cause mortality. SPPB scale showed the association with higher levels of mortality from serious cardiovascular and cerebrovascular events [81].

Conclusion
Frail population is a constantly growing group of patients with AMI. Early detection of frailty is considered as one of the essential factors in the achievement of better outcomes and the improvement in quality of life of older patients with AMI. Frailty is associated with high in-hospital mortality, hospital readmissions and worse outcomes. Frailty is a key prognostic factor of cardiovascular events in aged patients with AMI.

Frailty assessment provides valuable prognostic information for decision making in management of older patients with AMI who require focused care and early intervention. Thus, early detection of frail patients with AMI has the potential of improving decision making and proper distribution of healthcare costs. Timely evaluation of frailty is useful for healthcare practitioners as it enables the process of early identification of high-risk patients requiring an immediate attention in hospital and ambulatory setting as this group of patients might need more intensive secondary prevention and cardiac rehabilitation.

Discussed tools are widely used in scientific research and are regarded as effective and practical. Choice of a relevant frailty scale depends on personal preferences and its utility. There is no single widely accepted frailty assessment tool.

More research is needed for better management of frail patients with AMI. Tools, scales, and questionnaires discussed in this article can simplify this process and be valuable in clinical practice and further research.

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