Interplay and Causative Relationship Between Frailty and Atherosclerosis

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Abstract

Frailty syndrome is a complex condition with numerous contributing factors. It is characterized by a decline in physiological reserves and increased susceptibility to stress due to multi-system impairments. Commonly associated with aging, frailty can lead to adverse outcomes such as hospitalization, falls, and mortality. Cardiovascular diseases are recognized as a significant risk factor for frailty syndrome and frequently coexist in the elderly population. This review aims to explore the relationship between cardiovascular diseases and frailty syndrome. Research demonstrates that both acute and chronic cardiac conditions are prevalent among the risk factors for frailty. Cardiovascular diseases often manifest against the backdrop of atherosclerosis (AS) and are a leading cause of death in older adults. This review seeks to examine potential pathways through which cardiovascular events contribute to the development of frailty syndrome. Frail individuals often experience impaired physical function, significantly impacting their quality of life. Understanding the link between subclinical cardiovascular events and the pathogenesis of frailty syndrome is crucial for developing effective therapeutic interventions. Investigating how cardiovascular events influence the progression of frailty can provide valuable insights into improving clinical outcomes for frail patients.

Keywords: Frailty, Atherosclerosis, Cardiovascular disease

Significance | Frailty syndrome (FS) and cardiovascular diseases have a significant interaction, which impacts both the patient experience and how they are managed. Knowledge about the intricate associations between the two could provide a meaningful way towards developing targeted interventions.

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Introduction

Frailty is a complex clinical syndrome that can arise from various causes and factors. This condition is characterized by a decline in multiple bodily systems, resulting in lower physiological reserve and higher susceptibility to stress. It is commonly associated with the aging process and can lead to a range of negative consequences, including falls, hospitalization, institutionalization, and mortality (Chen et al., 2014).

In elderly patients, frailty syndrome (FS) often coexists with cardiovascular diseases such as CVD, CHD, HT, and cardiac failure. Individuals with FS typically experience more severe complications compared to those without the syndrome. Given the critical role of the circulatory system in physical functioning (PF), cardiovascular disease can increase the risk of FS and worsen its impact. Various risk factors and underlying physiopathological pathways contribute to the elevated risk of both cardiovascular disease and frailty (Wleklik et al., 2022).

Exercise and other interventions initiated at early stages can help reduce cardiovascular and frailty risks. Identifying individuals with a heightened cardiovascular risk early on can facilitate interventions that mitigate the development of frailty. However,

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research on the correlation between subclinical cardiovascular disease and FS remains limited (Fernandes et al., 2021).

There are specific cardiac markers, such as hs-cTnT and NT-proBNP, that can effectively detect subclinical cardiovascular disease. These markers can reveal myocardial damage and strain. While these markers are valuable, it is not yet fully understood whether they are the pathways through which cardiovascular disease contributes to the development of FS (Semeraro et al., 2021).

The origin of frailty: interplay between different pathologies

On the basis of FS's prognostic and epidemiological significance, a better understanding of its progression might assist in developing a therapeutic strategy. FS is a dynamic condition that potentially can be reversed. Multiple systems have been implicated in the development of FS, including the peripheral nervous system (PNS), related motor units, the brain, cardiovascular system (CV), immune system, voluntary muscles, and body fat (Menorca et al., 2013). The interaction of these systems collectively can also impact the pathogenesis of FS, although there is limited research on this topic so far. In Figure 1, we provided a scheme of the impact of various diseases on the development of frailty syndrome. Sarcopenia, characterized by degenerative muscle loss, is commonly observed in older patients, increasing the risk of functional disability, impaired mobility, and unintentional injuries (Larsson et al., 2019). Recent studies have indicated that muscle loss can accelerate the development of frailty syndrome in older individuals.

Aging has negative effects on brain morphology, resulting in reduced size, presence of microhemorrhages, and an increase in white matter hyperintensities (WMH). Alzheimer's disease, Parkinson's disease, and other degenerative conditions are prevalent in elderly patients, with Mild Cognitive Impairment (MCI) often coexisting with FS (Lecordier et al., 2021). Additionally, muscular innervation deteriorates with age due to motor neuron degeneration, leading to disability through the expansion of motor units. Moreover, with aging, there is a reduction in the number of motor units. These neural and muscular changes impair functionality in elderly individuals.

Immunosenescence predisposes older individuals to FS by causing dysbiosis, altering inflammatory responses, and accumulating senescent cells (Hepple et al., 2016). Elderly patients also tend to have higher body fat mass, both overall and in local internal organs. Metabolic disorders, excessive secretion of proinflammatory cytokines, and dysregulation of adipocytokines may elevate the risk of FS characterized by increased or unevenly distributed obesity (Waritu et al., 2024).

From a molecular signaling or microscopic perspective, FS involves the activation of abnormal tissue-specific pathways and the deterioration of repair pathways. We depicted the complicated interactions of molecular and cellular mechanisms leading to the frailty syndrome development on the Figure 2. Myopathy and potentially FS can result from skeletal muscle mitochondrial dysfunction, elevated levels of MAPK, phosphorylation, and the autophagy signaling pathway. On the other hand, the inhibition of inflammasome up-regulation, Nrf2, and NQO1 in neurons or astrocytes may improve cognitive function. In individuals with FS, osteoblasts often inhibit osteocalcin, RUNX2, and BMP2, leading to fractures, osteoporosis (OP), and physical impairments (Chen et al., 2022; Yan et al., 2022).

Immunological aging is linked to the suppressed JAK–STAT signaling pathway in white blood cells of individuals with FS. From a biological standpoint, cell senescence contributes to many aging-related symptoms. Cell senescence involves cytological processes such as mitochondrial dysfunction, excessive ROS production, telomere shortening, and depletion of stem cells, all of which can be observed in the tissues of FS patients. However, when interpreting experimental findings, it is important to consider the tissue-specific nature of related signaling pathways, as the molecules involved may exhibit different changes in various cells due to FS (Davalli et al., 2016).

CVD as a Risk Factor for Frailty

Heart failure, myocardial infarction (MI), atrial fibrillation (A-fib), valvular heart disease, and ischemic stroke are associated with an increased risk of FS. The Hospital Frailty Risk Score, which assesses the likelihood of FS based on ICD-10 codes, highlights the prevalence of codes related to acute and chronic heart diseases. While multiple pathways may play a role, one key pathway is that cardiovascular disease (CVD) diminishes physical activity levels and heightens the likelihood of physical impairments (Ruff et al., 2021).

Timely detection and treatment of heart conditions can potentially lower the incidence of FS by optimizing cardiac care. Examples include performing percutaneous coronary intervention (PCI) in individuals with angina, implanting biventricular pacemakers in patients with left ventricular failure, and intervening early in cases of valvular heart disease before symptoms worsen and frailty syndrome develops. Regular aerobic and resistance training can improve physical function and decrease the risk of FS (Reed et al., 2022).

Frailty as Risk Factor for Cardiovascular Disease

Frail patients are more prone to experiencing a heightened risk of numerous severe ailments. Linda Fried and her colleagues have reported that Frailty Syndrome (FS) significantly contributes to incidents of falls, mobility challenges, hospitalizations, institutionalizations, and mortality. Several recent studies have

corroborated the negative impact of FS on the health outcomes of elderly individuals (Fried et al., 2001).

Conversely, recognizing FS as a cardiovascular risk factor represents a novel concept. A recent meta-analysis on this topic revealed that across 10 cross-sectional studies, cardiovascular disease was more prevalent among individuals in both advanced and early stages of FS compared to those without it. Another meta-analysis synthesized data from six longitudinal prospective studies (Veronese, 2020). Following an average follow-up duration of 4.4 years, FS was strongly associated with a 70% higher risk of cardiovascular disease in advanced stages and a 23% increased risk in intermediate stages (pre-frailty), after adjusting for factors such as gender, age, and various comorbidities that could impact cardiovascular risk, including diabetes mellitus, hypertension, and obesity. The link between pre-frail stage, FS, and cardiovascular disease has been observed to have a greater impact on fatal events as opposed to non-fatal events, as noted by Veronese and his colleagues (Wong et al., 2018).

Individually, numerous studies have highlighted the association between cardiovascular events and FS. Khan and his team conducted research involving 2825 elderly patients aged between 70 and 79 years. The findings indicated that both mild frailty (HR 1.36, 95% CI 1.08-1.71) and advanced frailty (HR 1.88, 95% CI 1.02–3.47) were correlated with an elevated risk of cardiac failure (Adachi et al., 2022). A recent study by Sergi and co-researchers revealed that both the pre-frail stage and FS were linked to an increased cardiovascular risk in elderly Italian individuals who did not have limitations in their activities of daily living (ADLs) (Sergi et al., 2015). Furthermore, the AGES-Reykjavik Study highlighted that FS was associated with a 35% higher cardiovascular risk, with female patients exhibiting more pronounced results compared to male patients (Valsdóttir et al., 2022). This study delved into the assessment of subclinical cardiovascular disease markers, such as coronary artery disease (CAD) and increased carotid intima-media thickness (CIMT), thereby indicating an independent influence of FS on the progression of cardiovascular disease beyond initial atherosclerosis biomarkers. Collectively, these findings suggest that in elderly patients, FS may elevate the risk of cardiovascular diseases.

Inflammation and Frailty

Clegg and colleagues have highlighted that the decline in physical functioning that commonly occurs with aging can lead to a reduction in stress coping capacity, a condition often referred to as frailty (Clegg and Hassan-Smith, 2018).

Lang and colleagues have shown that pro-inflammatory cytokines can directly impact frailty by triggering protein degradation and indirectly affect major metabolic pathways (Lang et al., 2009). Newman and colleagues have identified a link between increased inflammation and frailty syndrome (FS), independent of existing chronic conditions, as evidenced by elevated levels of interleukin-6, C-reactive protein, fibrinogen, and antihemophilic factor (McKechnie et al., 2021). However, Yao and colleagues have reported that these markers may not be indicative of FS in older adults (Yao et al., 2019).

Recent research conducted on 23,910 elderly patients has revealed a correlation between the pre-frail stage, frailty, and heightened inflammation markers such as interleukin-6 and C-reactive protein (Soysal et al., 2016). Piggott and colleagues have stated that both FS and inflammation are associated with adverse outcomes in older patients, including physical impairment, hospitalizations, the onset of comorbidities, and mortality (Piggott and Tuddenham, 2020).

This meta-analysis has demonstrated a consistent link between inflammatory processes and FS, with individuals in frailty and pre-frailty stages exhibiting elevated levels of C-reactive protein, interleukin-6, tumor necrosis factor-alpha, leukocytes, and fibrinogen. These findings may be attributed to various factors (Baumeister et al., 2016). Firstly, individuals with frailty and pre-frailty may have more comorbidities that raise proinflammatory markers in the blood. Secondly, these individuals are more likely to have adiposity, especially in community settings, which can significantly increase proinflammatory markers, as noted by Greenberg and Obin (Greenberg and Obin, 2008), Veronese and colleagues (Veronese et al., 2022). Finally, Li and colleagues (Li et al., 2022) and Hubbard and Woodhouse (Hubbard and Woodhouse, 2010) have reported that individuals with FS often have a significantly weakened immune system, impaired T lymphocyte function, reduced antibody production, and increased oxidative stress products in mitochondrial function, leading to higher proinflammatory markers.

Fried and colleagues have indicated that older adults with FS exhibit higher levels of interleukin-6, tumor necrosis factor-alpha, and C-reactive protein compared to a control group of the same age (Fried et al., 2021). The increase in interleukin-6 levels is associated with slower walking speed and can predict a decline in walking speed over the medium term in elderly individuals living in the community. Individuals with activities of daily living (ADL) dysfunction display higher interleukin-6 levels in plasma compared to the control group. Several mechanisms may underlie the connection between FS and elevated inflammatory cytokines. Further research will enable us to explore the impact of many other processes that have yet to be investigated (Custodero et al., 2023).

Vasculopathy as a contributor to frailty and vascular tissue as a frailty-causing medium

The role of vascular tissue in the development of frailty syndrome (FS) is currently understudied. Atherosclerosis (AS) is a type of vasculopathy (VP) that is more prevalent in elderly individuals compared to the general population. Additionally, vascular calcification (VC) is commonly observed in the majority of healthy older adults. Recent research has revealed that cerebral VP and coronary VP are associated with a 41% and 21% increased risk of FS, respectively (Lee et al., 2020). Another finding indicates that aortic vascular calcification raises the risk of pre-frailty stage or FS by 5-10 times. Some studies have suggested that VP may elevate the risk of FS due to systemic inflammation (SI) and immunomodulating therapy (Demer and Tintut, 2008).

In elderly patients, vascular tissue is vulnerable to subclinical damage, which may lead to the development of FS. These patients often have various conditions such as hypertension (HT), diabetes, and dyslipidemia, which can contribute to vascular damage. Initial vascular injury can accelerate the progression of VP through biochemical changes (proinflammatory and pro-fibrotic stimuli) or physical impact (increased shear force due to flow turbulence) (Hardigan et al., 2016). Elderly individuals often use multiple therapeutic drugs to manage different conditions, and the use of multiple medications can increase vascular toxicity. Additionally, chronic low-grade inflammation (CLGI) commonly seen in elderly patients can also lead to vascular damage. Accumulation of subtle vascular injuries can result in dysfunction or structural changes in vascular tissues, ultimately contributing to the progression of FS (Dagli and Sharma, 2014).

Intrinsic factors underlying vascular susceptibilities to injuries

Vascular sensitivity to injuries can be influenced by various factors, including the senescence of vascular cells. Vascular tissues comprise perivascular adipocytes, endothelial cells (ECs), vascular smooth muscle cells (VSMCs), and adventitial fibroblasts (AFs). When exposed to reactive oxygen species and advanced glycation end products (AGEs), ECs exhibit a senescent phenotype, predisposing to the development of atherosclerosis (AS) (Kita et al., 2022). Mitigation of ECs senescence enhances endothelial function, reduces vascular permeability, improves repair capacity, and enhances the vasodilator response to nitric oxide. These biological changes manifest in variations in high blood pressure, vasomotor dysregulation, and autonomic dysfunction. Senescent VSMCs exhibit impaired growth and proliferation, particularly in response to local injuries in elderly adults (Tran et al., 2022). It is noteworthy that these individuals may display phenotypes that affect the ability of blood vessels to regenerate, a key factor in defining frailty syndrome. Senescent VSMCs also display a senescence-associated secretory phenotype (SASP), releasing proinflammatory cytokines that predispose individuals to AS. In elderly patients, VSMCs show signs of chronic low-grade inflammation (CLGI) and chronic inflammasome activation, a state known as "inflammaging" (Zha et al., 2022). Additionally, as VSMCs undergo senescence, their phenotype shifts from contractile to procalcific or synthetic, leading to increased vascular stiffness and reduced compliance, potentially resulting in changes in perfusion and organ failure. The presence of severe AS burden and high-risk plaque (HRP) features have been linked to an increased likelihood of frailty syndrome. Moreover, AFs exhibit pathological molecular changes that contribute to hypertension, particularly alterations in proteins related to mitochondrial function and inflammation (Lee et al., 2020). With aging, elastic arteries stiffen, and AFs experience oxidative stress due to increased levels of transforming growth factor beta 1 (TGF-β1). This results in the accumulation of adventitial collagen and medial calcification, both of which contribute to the age-related progression of vascular stiffness. Finally, perivascular adipocytes are believed to play a protective role against vascular damage by secreting anti-senescence and anti-inflammatory mediators locally. However, aging diminishes these protective effects and increases susceptibility to AS (Kim et al., 2018).

Oxidative Stress, Cardiovascular Diseases and Frailty—Common Links

Both frailty syndrome (FS) and cardiovascular risk seem to be linked to systemic inflammation (SI) and oxidative stress. There is thus a clear bi-directional relationship between FS and cardiovascular disease (Chianca et al., 2022).

Primarily, cardiovascular diseases are established as risk factors for FS. Studies by McNallan et al. (McNallan et al., 2013) and Polidoro et al. (Polidoro et al., 2013) have shown that various cardiovascular disorders can detrimentally affect functional abilities, leading to reduced physical activity, a hallmark of FS. Moreover, despite multiple recommendations, individuals with cardiovascular disease often decrease their physical activity levels unnecessarily, as highlighted by Stewart et al. (Stewart, 2019).

Secondly, individuals with FS face challenges in managing cardiovascular disorders. Research by Adabag et al. (Adabag et al., 2018) indicates that frail individuals have an elevated risk of both cardiovascular and non-cardiovascular mortality. Additionally, frailty is associated with increased complications following different cardiovascular interventions such as percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), and transcatheter aortic valve replacement (TAVR), as noted by Afilalo et al. (Afilalo et al., 2014).

Lastly, several shared risk factors between cardiovascular disease and FS, such as obesity, smoking, and an unhealthy diet, can predispose individuals to oxidative stress, as discussed by Stewart et al. (Stewart, 2019).

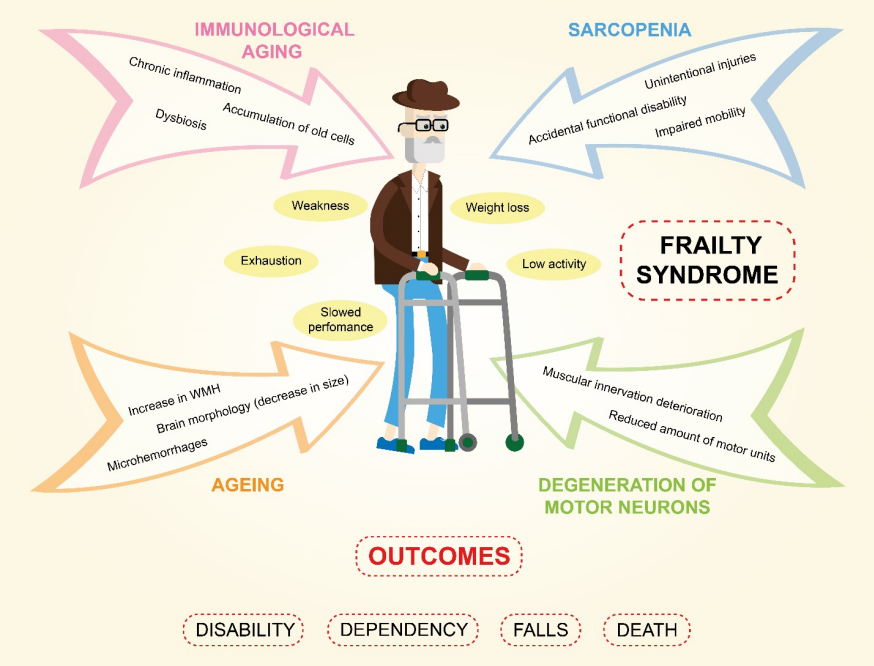

Figure 1. The contribution of various diseases and pathological conditions to the development of frailty syndrome

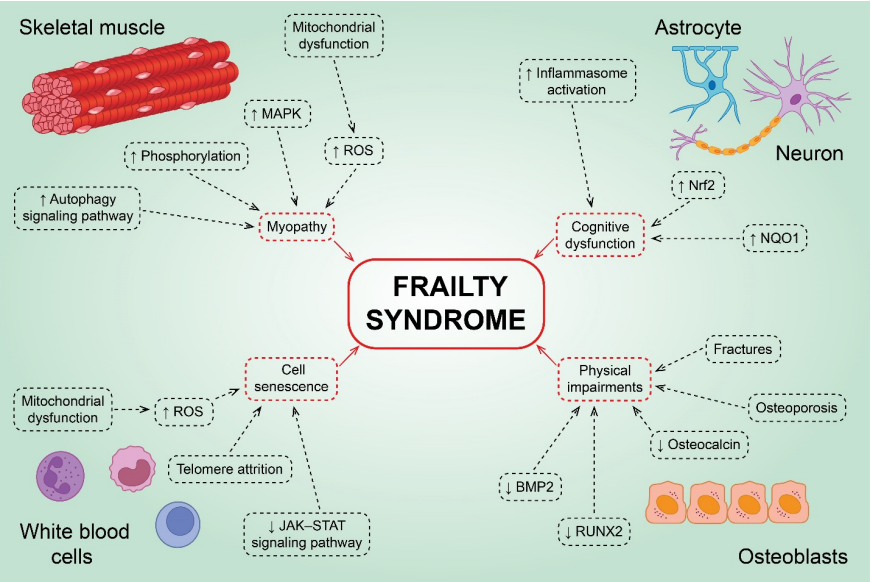

Figure 2. Molecular and cellular basis of frailty development

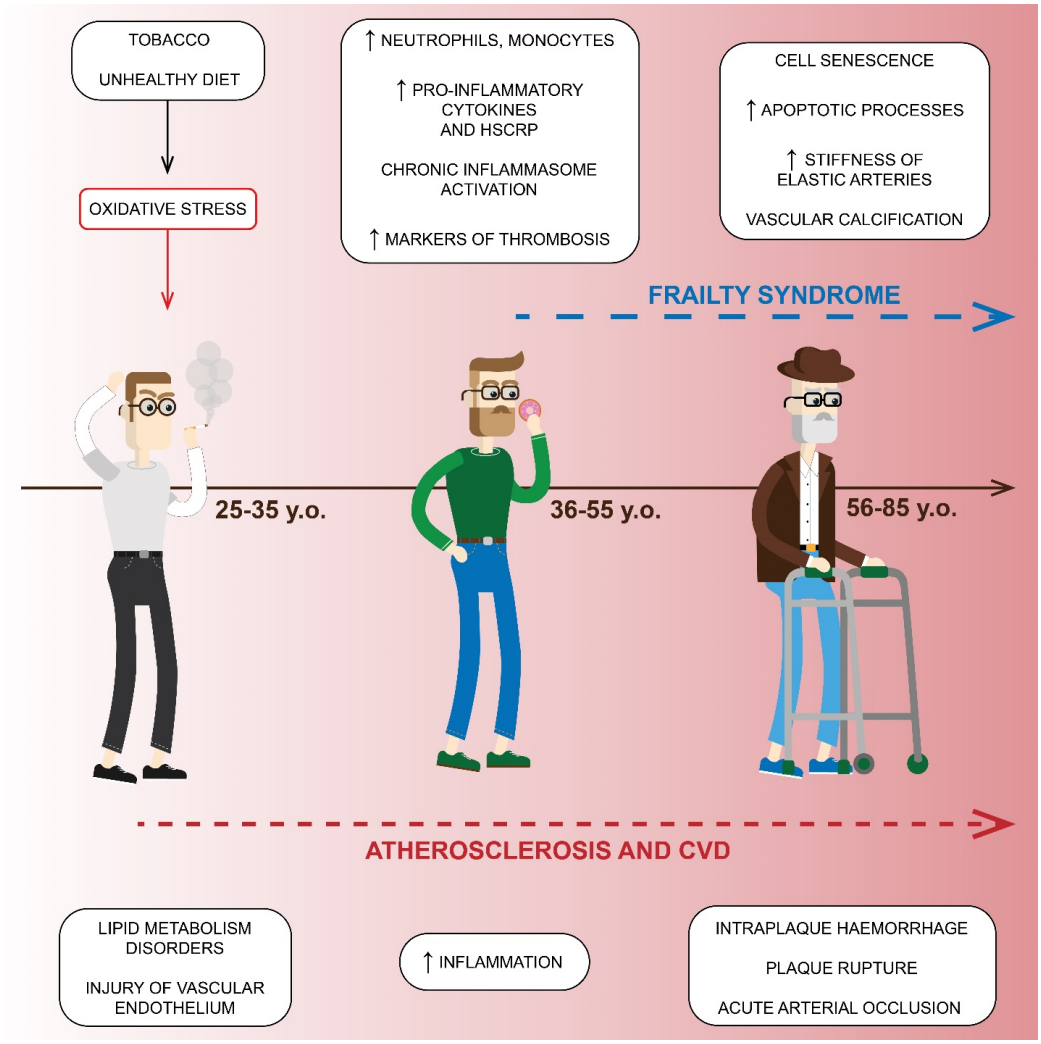

Figure 3. Common links between Frailty Syndrome, Cardiovascular Diseases and Atherosclerosis

Frailty and Cardiovascular Diseases Linked by Cellular Senescence

According to Soysal and colleagues, frailty syndrome (FS) and cardiovascular diseases share common features (Soysal et al., 2017). Therefore, it is reasonable to conclude that FS is a significant risk factor for cardiovascular diseases. Newman and colleagues conducted a large-scale epidemiological study that showed a correlation between FS and subclinical cardiovascular diseases (McKechnie et al., 2021). The Cardiovascular Health Study revealed that heart failure was eight times more prevalent in individuals with frailty syndrome compared to those without it. FS can weaken the resilience of heart tissue against various stress factors such as rhythm disturbances, volume or pressure overload, and myocardial ischemia, making it more susceptible to injury (Uchmanowicz et al., 2019). Nadruz and colleagues noted that cardiovascular diseases are more closely associated with the frail phenotype than with other conditions (Nadruz et al., 2017). Although the pathways leading to FS and cardiovascular diseases are complex, both are linked to chronic low-grade inflammation (CLGI). In both cardiovascular diseases and FS, levels of high-sensitivity C-reactive protein (hsCRP), interleukin-6 (IL-6), neutrophils, monocytes, and other proinflammatory markers in the blood are elevated, as reported by Cesari and colleagues (Cesari et al., 2017). Elevated levels of inflammation correlate with increased markers of thrombosis, potentially contributing to the pathogenesis of cardiovascular diseases. In addition to sharing common pathways, cardiovascular diseases seem to predispose individuals to frailty syndrome, as suggested by Dugravot and colleagues (Dugravot et al., 2020).

Atherosclerosis

In Figure 3, we proposed the various links between atherosclerosis and frailty syndrome through the aging. In elderly patients, one of the major causes of death is cardiovascular diseases, which often coexist with atherosclerosis (AS). Atherosclerosis is an inflammatory condition that progresses throughout life. Fulop and colleagues have indicated that the pathogenesis of atherosclerosis begins at a young age, and over the years, clinical manifestations develop in the form of coronary heart disease (CHD), peripheral artery disease (PAD), or cerebral arteriosclerosis (Anastasia et al 2024a, Anastasia et al 2024b, Anastasia et al 2024c). Atherosclerosis initiates in injured endothelial cells (ECs), which promote the deposition of LDL-C, leading to the oxidation of the vascular wall (Volpato et al., 2011). This triggers an acute inflammatory response resulting from the interaction between ECs and immune cells, both innate and adaptive, as reported by Libby and colleagues. Monocytes migrate to the tunica intima of the artery and differentiate into macrophages, initiating the release of proinflammatory cytokines such as interleukin-1 beta and interleukin-18 (Libby et al., 2019).

In the advanced stages, inflammation worsens due to cell senescence and apoptotic processes. According to Colin and colleagues, various adverse outcomes can occur, including intraplaque hemorrhage, plaque rupture, and acute arterial occlusion (Colin et al., 2014). Research by Ferrucci and Fabbri has shown that inflammatory markers like high-sensitivity C-reactive protein (hsCRP) and interleukin-6, which are indicative of cardiovascular disease risk, are elevated in adults and elderly patients, regardless of cardiovascular risk factors (Ferrucci and Fabbri, 2018).

It has been reported that lipid metabolism disorders, infections, proinflammatory cytokines, and the Heat-Shock Protein Axis are promoting factors in the pathogenesis of atherosclerosis. While increased concentrations of inflammatory agents in blood and tissues can contribute to the development of the disease, inflammation itself may also represent an existing pathological condition. However, none of these conditions alone can fully explain the connection between atherosclerosis and inflammation. Thus, when inflammation is present, multiple processes seem to contribute to the pathogenesis of atherosclerosis (Soeters et al., 2019, Anastasia et al 2023a, Anastasia et al 2023b).

Hormesis provides another perspective to understand the link between atherosclerosis and inflammation. It is a critical component of adaptability to counteract toxic external and internal agents. Hormesis can safeguard metabolism against irritants, thereby enhancing survival. Furthermore, it exhibits characteristics such as pleiotropy, generalizability, and a highly conserved state across biological models. It may help in defending against the progression of atherosclerosis, as it exerts a vasoprotective effect during age-related inflammation, starting from lipid-laden macrophages to atherosclerotic plaques (Schirrmacher, 2021). However, prolonged exposure to stressors can make the hormetic effect harmful (a phenomenon known as biphasic dose response), which increases the likelihood of clinical manifestations of atherosclerosis. As a result, hormesis is believed to indirectly contribute to inflammation. Processes of atherosclerosis to some extent occur in most older adults and may seem inevitable. However, clinical evidence supports the idea that these disorders can be mitigated in individuals with lower cardiovascular risk factors (Li et al., 2019).

Discussion and Conclusions

Frailty syndrome (FS) is a complex condition that often coexists with various pathological processes, including but not limited to cardiovascular diseases, chronic inflammation, and atherosclerosis. The relationship between these conditions and frailty is intricate and multi-faceted.

Cardiovascular diseases have been identified as a significant risk factor for the development of frailty. The impact of conditions such as atherosclerosis, an inflammatory disorder affecting blood vessels, on the pathogenesis of frailty is an area of growing interest. Atherosclerosis, being characterized by the buildup of plaque in arteries, could possibly contribute to the progression of frailty, especially in older individuals where vascular changes are more prominent.

In geriatric patients, atherosclerosis is observed more frequently compared to the general population, indicating a potential link between vascular health and frailty. However, the specific role of vascular tissue in frailty pathogenesis remains relatively understudied, prompting the need for further research to elucidate these mechanisms.

Elevated levels of pro-inflammatory cytokines have been associated with frailty syndrome, highlighting the influence of chronic inflammation on the development and progression of this condition. Understanding the various processes through which inflammation interacts with frailty is essential for developing targeted interventions.

Cardiovascular diseases and frailty share common causal pathways and are mutually reinforcing. Frail individuals often experience challenges in managing cardiovascular conditions, leading to increased risks of complications post-cardiac interventions and limitations in performing activities of daily living. Investigating the intricate relationship between vascular disorders and frailty will be crucial in advancing our knowledge and developing tailored strategies for the treatment and management of frail patients.

Continued research into the bidirectional relationship among atherosclerosis, cardiovascular diseases, inflammation, and frailty is imperative for improving clinical outcomes and enhancing the quality of life for individuals affected by frailty.

Author contribution

A.V.P. wrote, drafted; V.Y.G., V.N.S., A.N.O., R.V.G., D.F.B. wrote, reviewed, edited, VAK prepared the graph of the article. All authors have read and agreed to the published version of the manuscript.

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Competing financial interests

The authors have no conflict of interest.

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