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Frailty- and age-associated diseases: possibilities for intervention

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Frailty- and age-associated diseases: possibilities for intervention

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Editorial: Frailty- and age-associated diseases: possibilities for intervention

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Editorial on the Research Topic
Frailty- and age-associated diseases: possibilities for intervention

Introduction

Frailty, a complex and multifaceted syndrome characterized by reduced strength, endurance, and physiological function, has gained significant attention in recent years due to its profound impact on the aging population. As the global population ages, the prevalence of frailty and age-associated diseases has become a pressing public health concern. Frailty is characterized by a decline in physiological reserve and increased vulnerability to stressors, often followed by a cascade of health issues, including musculoskeletal disorders, cardiovascular diseases, metabolic alterations, and neurodegenerative conditions. These interconnected maladies significantly compromise the quality of life for older adults, posing challenges for healthcare systems and society at large. Central to the development of frailty and these diseases is the phenomenon of cellular senescence. This process, wherein cells enter a state of permanent growth arrest in response to stressors, such as oxidative damage and inflammation, contributes to the aging process and the onset of age-related pathologies. Senescent cells secrete pro-inflammatory factors, known as the senescence-associated secretory phenotype (SASP), which can disrupt tissue homeostasis and exacerbate chronic conditions. Consequently, targeting cellular senescence presents a promising avenue for intervention, potentially reversing or mitigating the impacts of frailty and associated diseases (Mylonas and O'Loghlen). This editorial synthesizes the insights from ten articles to establish the main hallmarks of current research and interventions in frailty management, highlighting the multidimensional strategies necessary for addressing frailty in older adults. The evidence from these articles collectively points toward a comprehensive approach that integrates exercise and rehabilitation, early detection, medication management, inflammation control, and individualized care.

The central role of exercise and rehabilitation in frailty reversal

One of the most consistent and well-supported interventions across the articles is the role of exercise in mitigating frailty and improving physical outcomes in older adults. Physical frailty is often associated with conditions such as sarcopenia, cognitive decline, and general mobility impairment, all of which can significantly impair an individual's independence and quality of life. Exercise-based interventions, particularly those involving multi-component programs, have the potential to reverse or delay the progression of frailty.

For example, structured physical activity programs that incorporate resistance training, balance exercises, and aerobic activities have shown significant benefits in reducing frailty scores, improving muscle mass, and enhancing physical function. Importantly, these interventions are often tailored to the specific needs of older adults, accounting for their capabilities and limitations. Rehabilitation programs designed for those recovering from strokes or other acute illnesses also demonstrate positive outcomes, highlighting the adaptability of exercise interventions across various medical conditions (Luo et al.).

One of the key benefits of exercise in frailty management is its ability to target multiple physiological systems. Resistance training, for instance, enhances muscle strength and function, addressing the muscle wasting commonly seen in sarcopenic individuals. Balance and mobility exercises, on the other hand, reduce the risk of falls, a major concern for frail older adults. Moreover, cardiovascular fitness improvements achieved through aerobic exercises help combat fatigue and increase overall endurance, providing a global approach to improving physical resilience.

The critical importance of early detection and screening

Frailty is often underdiagnosed or detected at advanced stages, when interventions may be less effective. Several articles emphasize the importance of early detection tools and screening methods in identifying frailty and related conditions, such as sarcopenia and osteoporosis, before they lead to debilitating consequences. This proactive approach to frailty management is crucial, as it allows healthcare providers to intervene before the condition progresses to a point where it severely compromises an individual's quality of life.

Among the screening tools mentioned, the SARC-F questionnaire is a widely recognized and practical instrument for assessing sarcopenia, one of the key contributors to physical frailty. The SARC-F assesses key aspects of muscle function, such as strength, assistance with walking, and difficulty standing from a chair. This tool has proven useful in both clinical settings and population-level screenings for identifying individuals at risk of muscle deterioration (Nguyen et al.; Valencia-Muntala et al.). Dual-energy X-ray absorptiometry (DXA) scans, commonly used to assess bone density, are also important for diagnosing osteoporosis, a condition closely linked to frailty due to the increased risk of fractures. Early identification of osteoporosis allows for timely interventions (Jianu et al.). Moreover, the competing risk nomogram developed for older patients with cancer emphasizes the value of predictive modeling in clinical practice. By identifying high-risk patients and intervening early, clinicians can enhance prognostic accuracy and guide treatment plans, ultimately improving patient outcomes (Wu et al.).

The integration of screening tools for sarcopenia, osteoporosis, and cancer into standard geriatric care is critical for preventing the downward spiral of frailty.

Medication management and poly-deprescribing as key interventions

Polypharmacy, or the concurrent use of multiple medications, is another significant concern in the management of frailty and age-associated diseases. Many older adults are prescribed a range of medications to manage chronic conditions such as hypertension, diabetes, and cardiovascular diseases. However, the simultaneous use of multiple drugs can lead to adverse drug reactions, cognitive impairment, and decreased physical function, all of which contribute to frailty.

A key finding across the articles is the importance of poly-deprescribing, a process that involves the careful reduction or discontinuation of unnecessary medications in older adults. Deprescribing strategies have been shown to improve outcomes such as cognitive function, reduce the risk of falls, and enhance overall wellbeing. This process must be handled with care, as abrupt cessation of essential medications can have negative consequences. Therefore, the deprescribing process should involve a comprehensive review of each patient's medications, with a focus on maintaining the most beneficial treatments while eliminating those that contribute to frailty or increase the risk of adverse events (Garfinkel and Levy).

Also, the use of conventional, herb-based medicine can be a potential therapeutic intervention for frailty but also a preventive method (Amitani et al.) for mild and moderate frailty.

The role of inflammation and comorbidity management in frailty

Frailty is closely linked to chronic inflammation and the presence of multiple comorbidities, such as diabetes, cardiovascular disease, and neurodegenerative conditions like Parkinson's disease. Chronic low-grade inflammation, often referred to as "inflammaging," is a hallmark of aging and has been implicated in the development of frailty. Inflammation contributes to muscle wasting, cognitive decline, and increased vulnerability to infections and other stressors, all of which can accelerate frailty.

Addressing the inflammatory burden in frail individuals is, therefore, a crucial component of frailty management. Anti-inflammatory interventions, whether through pharmacological agents or lifestyle modifications such as diet and exercise, can help reduce the impact of systemic inflammation on physical and cognitive function. Some studies have explored the use of anti-inflammatory drugs, such as nonsteroidal anti-inflammatory drugs (NSAIDs) or more targeted therapies, to reduce frailty in older

adults, although more research is needed to determine the long-term efficacy and safety of these approaches (Merchant et al.).

Additionally, managing comorbid conditions that contribute to inflammation and frailty is essential for improving outcomes in older adults. For example, optimal management of diabetes through glycemic control can prevent complications such as neuropathy and cardiovascular disease, both of which exacerbate frailty (Komici et al.). By taking a synergistic approach to inflammation and comorbidity management, healthcare providers can help mitigate the impact of these factors on frailty progression.

Conclusion

The management of frailty and age-associated diseases requires a comprehensive, multifactorial approach that integrates exercise, early detection, medication optimization and inflammation control, and individualized care. The findings from these ten articles highlight the importance of targeting both the physical and cognitive components of frailty, addressing underlying comorbidities, and tailoring interventions to each individual's unique needs. By adopting a proactive and personalized approach to frailty management, healthcare providers can improve outcomes for older adults and help them maintain independence and quality of life as they age. The future of frailty research and clinical care lies in further refining these strategies to create a robust framework for managing frailty in an increasingly aging population.

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Cellular Senescence and Ageing: Mechanisms and Interventions

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The influence of the activation of a cellular phenotype termed senescence and it's importance in ageing and age-related diseases is becoming more and more evident. In fact, there is a huge effort to tackle these diseases via therapeutic drugs targeting senescent cells named senolytics. However, a clearer understanding of how senescence is activated and the influence it has on specific cellular types and tissues is needed. Here, we describe general triggers and characteristics of senescence. In addition, we describe the influence of senescent cells in ageing and different age-related diseases.

Keywords: senescence, ageing, SASP, age-related disease, hallmarks, senolytics, senomorphics, extracellular vesicles

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INTRODUCTION

Multicellular organisms have been living on our planet for over 750 million years. Multicellularity is a very efficient way of living, as tasks for survival are divided into different cell types. A plant, for example, has different specialized cell types, each regulating a special function, such as taking nutrients from the soil, photosynthesising, or creating a hard trunk for protection. This successful coordination is accomplished due to a simple principle, i.e., the survival and well-being of the multicellular organism are more important than the survival of any individual cell (Michod, 2007; Pichugin et al., 2019).

When a single cell malfunctions, it can potentially harm the whole multicellular organism. There are two ways of controlling such incidences. The first is based on the ability of specialised cells to recognise the malfunctioning cell and destroy it. The second way is based on the ability of the cell to recognize its own dysfunction and cause its own death and/or limit its ability to grow. Mechanisms combining both ways of elimination are used in most cases (Michod, 2007; Pichugin et al., 2019). The induction of cellular senescence is an example of such mechanisms occurring in mammals. First, by recognizing its own dysfunction and inducing a stable cell cycle arrest via activation of cell cycle inhibitors such as $p16^{INK4A}$ and $p21^{CIP1}$. Second, by discharging signals to the immune system so that it recognises and destroys the damaged - senescent – cell (Lee and Schmitt, 2019).

The presence of senescent cells has both beneficial and detrimental effects on the organism. On the one hand, senescence has beneficial outcomes, especially during the early stages of development. Senescence occurs in many different locations during the development of the mammalian embryo and is responsible for the appropriate tissue remodeling and the elimination of unwanted cells as the tissues develop (Munoz-Espin and Serrano, 2014). Senescence is also responsible for beneficial outcomes on the adult organism. For example, it regulates proper wound healing by limiting the development of fibrotic tissue. Senescence induction in myofibroblasts prevents the upregulation of matrix degrading components and creates an anti-fibrotic microenvironment, contributing to normal tissue healing (Jun and Lau, 2010). This mechanism is also conserved during fibrosis in

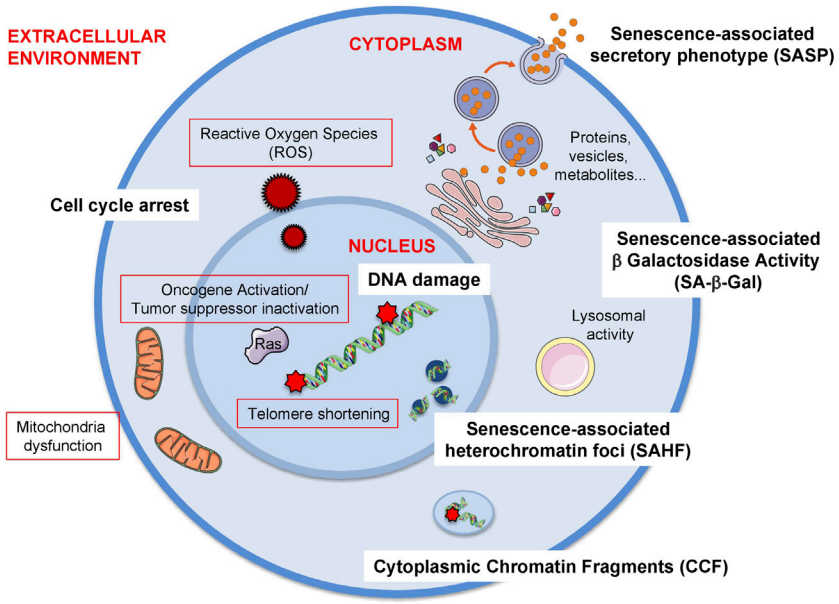

FIGURE 1 | Triggers and biomarkers of cellular senescence. There are several stimuli or triggers that activate cellular senescence (red outline). Some of these are depicted in the figure such as the formation of Reactive Oxygen Species (ROS) both from external factors or internal such as mitochondrial dysfunction. Others include the expression of certain oncogenes, e.g., RAS (Rat sarcoma virus) or the loss of tumour suppressor genes, e.g., PTEN (Phosphatase And Tensin Homolog). The shortening of telomeres due to the lack of telomerase enzyme also elicits cellular senescence. Additionally, mitochondrial dysfunction, which can be due to mitochondrial malfunction, increase in mitochondrial size or mass, mitochondrial fusion or mitochondrial fragmentation can also induce senescence. As there is no gold standard biomarker of senescence, a combination of several biomarkers are used to identify this cellular phenotype both *in vitro* and *in vivo*. Some of these biomarkers are the release of a senescence-specific secretome, the senescence-associated phenotype (SASP) formed by proteins, vesicles, metabolites. Other biomarkers the presence of DNA damage and the establishment of a stable cell cycle arrest. Furthermore, chromatin alterations such as heterochromatin foci (senescence-associated heterochromatin foci, SAHF) or the presence of chromatin in the cytoplasm (cytoplasmic chromatin fragments, CCF) are also present during senescence. Finally, the most extensively used biomarker of senescence is the presence of senescence-associated -β- galactosidase activity (SA-β-Gal) which is due to an increase in lysosomal activity, although it is important to take into account that this feature is not exclusive of senescent cells.

many tissues (Munoz-Espin and Serrano, 2014). On the other hand, senescence is thought to be one of the reasons cell tissues age and overaccumulation of senescent cells usually promotes accelerated biological ageing and age-related diseases, leading to the overall ageing of the organism (van Deursen, 2014). It is hypothesized this is due to either an aged immune system, which inefficiently eliminates senescent cells from tissues, or due to an incompetent SASP released by senescent cells. It is probable that a combination of both, together with other unknown factors, are implicated in the detrimental effects of the accumulation of senescent cells.

TRIGGERS OF SENESCENCE

Senescence can be triggered by a variety of stresses including but not limited to telomere shortening, oncogene activation and the presence of reactive oxygen species (**Figure 1**).

Telomere Shortening

Telomeres are heterochromatic repeated sequences of nucleotides at both ends of human chromosomes, consisting of 8–12 kilobases at birth. With each DNA replication, 50–200 base pairs of telomeres are lost from each human cell, due to the inability of DNA polymerase to replicate the whole molecule. Telomeres shorten with each cell division until they reach a critical point. As a result, a DNA damage response (DDR) is elicited, which in turn increases $p16^{INK4A}$ and $p21^{CIP1}$ cellular levels finally promoting senescence (Di Micco et al., 2021). This type of senescence is called replicative senescence because it originates from the number of replications a cell line undergoes (Deng et al., 2008; Fafian-Labora and O'Loghlen, 2020).

Oncogene Activation

Oncogene overexpression and tumour suppressor gene inactivation promote oncogene-induced senescence (OIS). Oncogenes are mutated forms of normal genes present in the human genome, called proto-oncogenes. Under normal circumstances, these genes regulate physiological functions favourable to the cells, but when mutated by gene overexpression or amplification they have the potential to promote cancer development. Tumour suppressor genes code for proteins regulating pathways that contribute to the prevention of cancer development. Thus, their loss of function leads to the loss of these cancer-protective properties, causing cancer. Oncogenes known to be overexpressed in OIS include RAS, BRAF, AKT, E2F1 and cyclin-E. Tumour suppressor genes

commonly lost in OIS are PTEN and NF-1 (Gil and Peters, 2006; Perez-Mancera et al., 2014; Lee and Schmitt, 2019).

Mitochondrial Dysfunction

Reactive oxygen species (ROS) is a group of molecules, including hydrogen peroxide (H_2O_2), superoxide ion ($O_2^{\bullet-}$) and hydroxyl radical ($^{\bullet}OH$). They are products of oxidative metabolism in mitochondria, usually scavenged by the enzyme superoxide dismutase (SOD). When mitochondria malfunction, ROS are released causing oxidative damage to mitochondrial and cellular DNA (Desdin-Mico et al., 2020; Di Micco et al., 2021; Martini and Passos, 2022). ROS can also form from the interaction of exogenous factors, such as UV radiation and chemicals from tobacco, and damage cellular DNA. These reactions signal a DDR similar to that caused by telomere shortening, activating $p21^{CIP1}$ and $p16^{INK4A}$ and causing senescence (Di Micco et al., 2021; Prasanna et al., 2021).

HALLMARKS OF SENESCENCE

Senescence is a cellular state that can be induced by different stimuli and it is characterised by a stable cell cycle arrest, a secretory-associated phenotype (SASP), macromolecular damage, deregulated metabolism and characteristically-altered cellular morphology. However, as no single marker of senescence is reliable, a combination of markers must be used to identify the senescence phenotype (Sharpless and Sherr, 2015; Gorgoulis et al., 2019) (**Figure 1**).

Cell Cycle Arrest

Triggers of senescence activate specific alterations in intracellular pathways to achieve a stable cell cycle arrest. It can be initiated from the *INK4A-ARF* locus, present on chromosomal region 9p21, containing the tumour suppressor genes *INK4A* and *ARF*. Gene expression of the locus is normally silenced by Polycomb Repressive Complexes 1 and 2 (PRC1 and 2). PRC1/2 disruption causes gene activation and transcription of two proteins: $p16^{INK4A}$ and $p14^{ARF}$. Such disruptions are associated with cancer development and trigger oncogene-induced senescence to prevent it (Gil and O'Loghlen, 2014). $p16^{INK4A}$ inhibits the action of the Cyclin-Dependent kinase (CDK4/6) complex, which also hampers phosphorylation of retinoblastoma (Rb) establishing cell cycle arrest (Herranz and Gil, 2018). Finally, $p14^{ARF}$ is also encoded from the *INK4A-ARF* locus and acts by inhibiting Mouse Double Minute-2 homolog protein (MDM2) that activates p53, furtherly promoting cell cycle arrest (Herranz and Gil, 2018).

Furthermore, after DNA damage, two serine/threonine kinases are activated, named Ataxia-Telangiectasia Mutated (ATM) and ATM- and RAD3-related Protein (ATR). These kinases activate Checkpoint Kinases-1 and -2 (CHK-1 and -2), which in turn phosphorylate p53. This is a transcription factor normally bound to MDM2, a ubiquitin-ligase enzyme that tags p53 for degradation by proteasomes. Phosphorylation of p53 causes its release from MDM2, creating a stable and active form of p53, free to travel in the nucleus and upregulate *CDKN1A* transcription and, thus, $p21^{CIP1}$ induction. $p21^{CIP1}$ protein then acts as a CDK inhibitor, blocking G1/S phase cell cycle CDKs, a complex of Cyclin E and CDK2, and S phase CDKs, a complex of Cyclin A and CDK2 or CDK1. CDK2 is a kinase responsible for the phosphorylation of Rb and subsequent inactivation of this protein. This enables the E2 transcription factor (E2F) to regulate the genes needed to promote cell cycle progression. Inhibition of CDK2 hampers the phosphorylation of Rb which traps E2F avoiding the interaction with its target genes and finally establishing cell cycle arrest (Herranz and Gil, 2018).

Macromolecular Modifications

Senescence is characterised by specific forms of macromolecular damage, for example telomere-associated foci (TAF). DNA damage in TAF is linked to senescence and is expressed by increased phosphorylation of histone-2, in the form of γ-H2AX within telomeres (Martini and Passos, 2022). During senescence, senescence-associated heterochromatin foci (SAHF) can also be formed, characterised by dense chromosomes, concentrated in a single nucleolus and bound to hypoacetylated histones and heterochromatin proteins, like HP1. This chromosomal arrangement in this focus causes the silencing of the expression of the corresponding genes, in particular E2F target genes involved in cell cycle progression (Narita et al., 2003).

Cytoplasmic chromatin fragments (CCFs) are fragments of chromatin present outside the nucleus that are formed via a nuclear-cytoplasmic blebbing process (Ivanov et al., 2013). CCFs induce an innate immune response by activating the cytosolic DNA sensing cyclic GMP–AMP synthase (cGAS)-STING pathway (Dou et al., 2017; Gluck et al., 2017). This in turn promotes the SASP via activation of the NF-κB pathway, leading to a pro-inflammatory response (Vizioli et al., 2020; Miller et al., 2021).

Secretory Phenotype

Senescent cells characteristically affect their surrounding tissue by secreting substances, grouped under the term senescence-associated secretory phenotype (SASP). This secretion is regulated by pathways involving the protein kinase p38MAPK and the transcription factor nuclear factor kappa beta (NF-κB). The secreted substances include soluble, growth and extracellular matrix (ECM)-remodeling factors, although recently other components such as extracellular vesicles and metabolites have been found (Fafian-Labora and O'Loghlen, 2020). They act by either reinforcing or spreading senescence to surrounding cells and activating immune responses for cell clearance. Soluble factors include interleukins (IL) 1α, 1β, 6, 7, 8, 13 and 15, and chemokines, such as monocyte chemoattractant proteins (MCP) 2 and 4, macrophage inflammatory proteins (MIP) 1a and 3a, and eotaxin. Such factors recruit immune cells to clear senescent cells. Growth factors include, among others, insulin-like growth factor (IGF), epidermal growth factor (EGF), fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF) and angionenin. These factors signal pathways regulating cell growth and angiogenesis, and in such microenvironments, they contribute to senescence (Coppe et al., 2010). ECM-

remodeling factors, such as matrix metalloproteinases (MMP), ADAMTS proteins and integrins also contribute to senescence. They act by altering ECM components, like collagen, and promote ECM degradation. This disrupts the normal crosstalk between cells and disorganizes their physical attachments, contributing to senescence. ECM disruption also aids in immune cell recruitment (Rapisarda et al., 2017; Fane and Weeraratna, 2020; Levi et al., 2020).

Extracellular vesicles are lipid membrane vesicles released by either pinching of the cytoplasmic membrane of the cell or formed upon activation of the endocytic pathway (van Niel et al., 2018). They contain a variety of proteins, nucleic acids, metabolites and lipids that decide their course of action and functionality in recipient cells (Tkach and Thery, 2016; O'Loghlen, 2018; O'Loghlen, 2022). They have been recently identified as part of the SASP mediating both paracrine senescence in different contexts (Borghesan et al., 2019; Jeon et al., 2019) and rejuvenation of different tissues in aged mice (Yoshida et al., 2019; Fafian-Labora et al., 2020; O'Loghlen, 2022).

Metabolites are an emerging part of the SASP and are discussed in the next section (Fafian-Labora and O'Loghlen, 2020; Smith et al., 2020).

Deregulated Metabolism

Normal metabolism of the cell is also affected in the state of senescence leading to altered metabolite phenotypes (Smith et al., 2020). For example, the biosynthesis of leukotrienes is enhanced during senescence leading to their enrichment in the SASP which in turn promote lung fibrosis (Wiley et al., 2019). Importantly, it has been recently described that prostaglandin D2 is a useful biomarker to determine the efficacy of drugs that selectively eliminate senescent cells (termed senolytics) (Wiley and Campisi, 2021; Wiley et al., 2021).

As mentioned, malfunctioning mitochondria and anomalies in oxidative phosphorylation (OXPHOS) are characteristic of senescence (Dorr et al., 2013). Specifically, there is an increase in mitochondrial membrane potential during senescence that correlates with an increase in ROS production. This was partially described to be due to an increase in the expression of fatty acid synthase (FASN) (Fafian-Labora et al., 2019). Furthermore, senescence can cause mitochondria to alter their normal morphology. Examples include an increase in mitochondrial size and mass, mitochondria fusing together and fragments of mitochondria accumulating (Helman et al., 2016; Borghesan et al., 2019). In fact, mitochondrial dysfunction-associated senescence (MiDAS) is mainly driven by accumulation of NADPH in the cytoplasm, lowering NAD^+/NADPH ratio, ATP levels and activating AMPK (Wiley et al., 2016). Furthermore, mitochondria elimination by mitophagy prevents both the cell cycle arrest and release of the SASP (Correia-Melo et al., 2016). Interestingly, functional mitochondria can be trafficked via extracellular vesicles, adding a layer of complexity to their role in cellular biology (Peruzzotti-Jametti et al., 2021).

Cellular granularity is a term used for any dense substance accumulating in cells and is a result of deregulated metabolism. Specifically, in senescence, lysosomal parts, protein aggregates such as amyloid-beta and proteolysed histones, and vesicles used for exocytosis are the main components of this granularity. In specific cell-types, like liver and muscle cells, glycogen granules are also highly abundant during senescence (Kwon et al., 2019).

SENESCENCE IN PATHOLOGY

Cells from each cell-type have a specific number of divisions, a principle called the Hayflick Limit (Hayflick and Moorhead, 1961). Stem cells have a larger cell-division capacity than differentiated cells. This is because they contain an enzyme, called telomerase, reversing telomere loss in each replication. Through human life-time, stem cells differentiate into tissue-specific cells to replace damaged cells. However, when stem cells reach their limit, they also undergo senescence and the tissue starts to age. Apart from ageing, early-onset of senescence due to oncogene activation or increased ROS formation causes disease (Munoz-Espin and Serrano, 2014). Here, we will discuss the implications of cellular senescence during ageing and in age-related pathologies (**Figure 2**).

Ageing

Senescent cells increase in numbers as the organism ages. Such accumulation of senescent cells may impact on ageing through two possible mechanisms. First, the accumulation of senescent cells in tissues may disrupt tissue functionality, and, second, senescence may limit the regenerative potential of adult stem cells by disrupting the normal regulation of the stem cell niche within the tissue (van Deursen, 2014).

As mentioned previously, senescent cells secrete factors acting as paracrine signals to nearby cells and spreading senescence. These paracrine signals activate the recruitment of immune cells creating an inflammatory microenvironment (Fane and Weeraratna, 2020; Di Micco et al., 2021). Senescent signals not only damage proliferative cells but also stem cells inducing their rapid and abnormal differentiation into committed cells with dysfunctional characteristics (Paul et al., 2021). Additionally, during tissue repair, some parts of the tissue are replaced with fibrous materials in a process called tissue fibrosis in which the activation of senescence is crucial (van Deursen, 2014).

Diseases of the ageing population become more common, as human lifespan increases. Osteoarthritis, idiopathic pulmonary fibrosis, atherosclerosis and Alzheimer's disease are, among others, characteristic examples of age-related diseases where senescence activation has been observed (McHugh and Gil, 2018).

Osteoarthritis

Osteoarthritis is an age-related disease of cartilage loss in joints. Chondrocytes, the main cells in cartilage, are shown to undergo senescence. This is evident as osteoarthritic chondrocytes express $p16^{INK4A}$ and the surrounding tissue within the affected joint has high concentrations of IL-1, IL-6 and MMP-3. In current research, procedures aiming to remove senescent cells from the tissue are being tested as a treatment option (Jeon et al.,

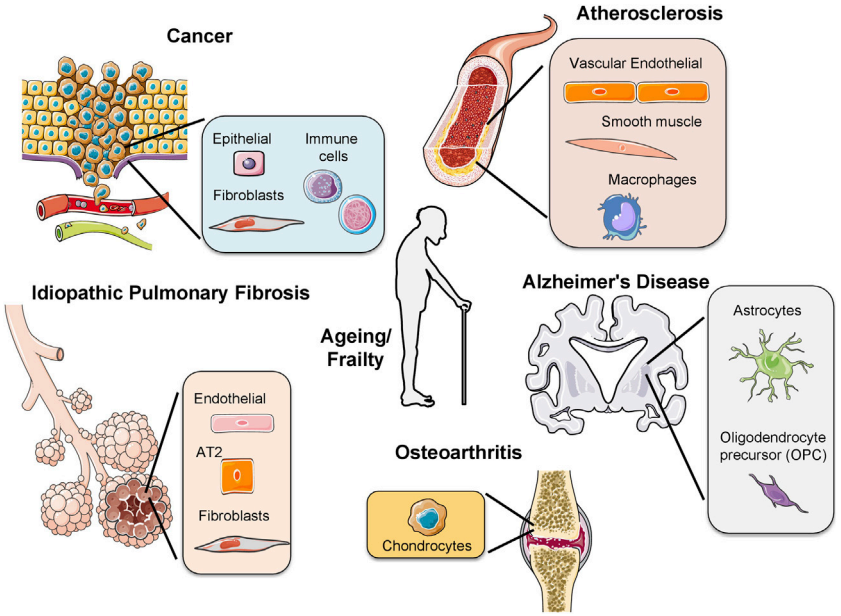

FIGURE 2 | Activation of senescence in different age-related pathologies. The presence of senescent cells has been observed in different diseases, for example, osteoarthritis, idiopathic pulmonary fibrosis, cancer, atherosclerosis, Alzheimer's disease and during frailty. In each disease different cell types undergo senescence. In cancer several immune cells from different origins as lymphoid or myeloid undergo senescence. AT2: alveolar type 2 cells.

2017; Coryell et al., 2021). Such processes are grouped under the term "senolysis" (Kelly, 2017; Dolgin, 2020). Furthermore, there is a group of drugs called "senomorphics" that act by targeting SASP factors, neutralising or inhibiting their actions (Gasek et al., 2021). For example, in mouse models for osteoarthritis, UBX0101 was used as an inhibitor for the MDM2/p53 interaction. The drug was able to eliminate the mice's senescent chondrocytes providing some evidence for senomorphics as a future therapeutic option for osteoarthritis (Zhang et al., 2022).

Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis (IPF) is a lung disease, correlated with advanced age in incidence and severity. The median survival is 2–3 years. Three different cell types have shown positive senescent markers in IPF: alveolar type 2 cells (AT2Cs), endothelial cells and fibroblasts. Such markers include $p21^{CIP1}$, $p16^{INK4A}$ and SA-β-Gal. AT2Cs are progenitor cells capable of self-renewal and differentiation into alveolar type 1 cells. Thus, they cause structural alterations in tissue architecture with each regeneration, contributing to disease. Fibroblasts are also important cells in the lungs, responsible for producing and maintaining the ECM. Thus, senescent fibroblasts remodel ECM and create a senescent microenvironment, furtherly progressing the severity of the disease (Schneider et al., 2021). Senomorphics have also been studied *in vitro* to show whether they can act as a therapeutic option for IPF. Specifically, the macrolide antibiotic roxithromycin managed to block the TGFβ stimulation, an important component of SASP, preventing further senescence induction to lung fibroblasts (Zhang et al., 2021).

Atherosclerosis

Atherosclerosis is a disease of human arteries, where a fatty streak is formed and occludes the vessel. The development of atherosclerosis is related to the presence of oxidised low-density lipoprotein (LDL) in the vessel wall, chronic inflammation and malfunctioning vascular endothelial cells. Vascular endothelial cells in atherosclerotic coronary arteries have shown positive SA-β-Gal activity and expression of $p21^{CIP1}$ and $p16^{INK4A}$, suggesting that they undergo senescence. Senescence creates a leaky and highly permeable endothelium, allowing macrophages and other immune cells to enter. Macrophages have a crucial role in atherosclerosis. They enter the ECM of the vessel wall, induce ECM degradation and absorb the oxidised LDL, becoming part of the fatty streak. Smooth muscle cells in vessels also undergo senescence, enhancing the hazardous microenvironment by their SASP and forming the necrotic core of the fatty streak. Finally, the recruitment of monocytes and macrophages by SASP, and the high abundance of senescent macrophages in the organism are both contributing to atherosclerosis progression (Minamino et al., 2002; Bennett and Clarke, 2016; Bennett and Clarke, 2017). Drugs with senomorphic properties have also been studied for their effectiveness into treating atherosclerosis. For example, drugs like rapamycin and ruxolitinib inhibit intracellular mediators, such as the kinase mTOR, that play a key role in SASP initiation (Ramírez et al., 2022).

Alzheimer's Disease

Alzheimer's disease is characterised by extracellular deposition of amyloid-beta (Aβ) plaques. As mentioned above, amyloid-beta is part of the protein aggregates that form in senescent cells.

Astrocytes, cells responsible for regulating the homeostasis of the neurons and maintaining the blood-brain barrier, are involved in the pathology of the disease. Astrocytes expressing $p21^{CIP1}$, $p16^{INK4A}$ and active SA-β-GAL are related to an increased Aβ plaque formation. Specifically, senescent astrocytes and their SASP limit the clearance of Aβ deposits by microglia. Also, exogenous application of Aβ oligomers can trigger astrocytes to undergo senescence. Additionally, SASP from astrocytes can induce neurofibrillary tangle formation in neurons, another common feature of Alzheimer's disease. In addition, the presence of senescence markers has also been observed in oligodendrocyte progenitor cells (OPCs) where treatment with senolytics alleviates cognitive deficits in an Alzheimer's disease model (Zhang et al., 2019). Altogether, these results suggest there is a connection between senescence and Alzheimer's disease pathogenesis (Saez-Atienzar and Masliah, 2020; Guerrero et al., 2021). Senomorphic agents against Alzheimer's disease have been studied even in human trials. For example, dasatinib and quercetin have been shown to interact with AKT, an important protein involved in the regulation of the SASP (Zhang et al., 2022).

Frailty

Frailty is a clinical state characterised by a low overall physical activity, a decline in multiple physiological systems and an increased vulnerability to stress-inducing factors mostly resulting from physiological ageing. It is associated with -but not defined by- increased chronological age and multiple comorbidities. The frail phenotype presents mainly with a noticeable decrease in muscle strength, general weakness, a significant decrease in walking speed, unintentional weight loss and reports of exhaustion (Fried et al., 2001).

Senescence is associated with the pathophysiology of many chronic conditions that are considered as variables for assessing a Frailty Index, such as Alzheimer's disease. Furthermore, the frail phenotype can also be considered as a result of cellular senescence (LeBrasseur et al., 2015). Systemic inflammation is one of the main reasons that frail individuals feel general weakness and exhaustion. Accumulation of senescent cells is known to dysregulate the response of the immune cells present in the tissue's microenvironment and cause significant changes to the secretions of inflammatory factors. For example, IL-6 and TNF-α secretions by senescent and immune cells are increased in aged tissues and their receptors are upregulated on various cell types. When this pathophysiological response is repeated several times and in multiple tissues, the individual reaches a long-term unresolved chronic inflammatory state which acts as a precipitant of frailty (Sathyan et al., 2020). Additionally, the decline in strength can also be attributed to senescent cells disrupting the normal neuromuscular physiology. Muscle mass loss (sarcopenia) and denervation or neuron loss within neuromuscular junctions are mostly due to increased senescence induction and insufficient clearance of senescent cells (Sousa-Victor et al., 2021). Finally, senescence resulting in inflammation and deterioration of brain function causes mental decline contributing to the inability of a frail individual to perform everyday tasks (Guerrero et al., 2021). Senescence induction in the neurons, the brain's immune cells and the vascular cells of the brain's blood vessels result in the development of neurologic and psychological conditions causing disorientation, difficulty with planning, mood and personality changes, emotional decline and many other symptoms that decrease the person's ability to perform simple tasks.

In conclusion, it is important to make clear that senescence is what many use to define physiological ageing, the biggest contributor to frailty. Physiological age differs from chronological age, which is simply the number of years a person is alive. Physiological age is a result of environmental, genetic and epigenetic factors that lead to the ageing of tissues and the deterioration of their functions, which progressively causes the individual to reach the state of frailty.

Cancer

Cancer is a disease affecting 17 million people every year and is responsible for 9.6 million deaths. Cancer arises from a single cell that undergoes several mutations in genes regulating cell proliferation and division. This cell then grows and divides indefinitely, forming a three-dimensional structure, the tumour. Cancerous cells compete with healthy cells for resources and they succeed due to their advantageous mutations favouring cell cycle progression (Hanahan and Weinberg, 2011; Leite de Oliveira and Bernards, 2018).

Senescence has a crucial role in preventing cancer development. Cancer cells must proliferate rapidly and indefinitely. Thus, a stable cycle-arrest causes restriction of tumour growth and prevention of further cell division. The SASP also contributes to anti-tumour activity. It facilitates the recruitment of immune cells through the expression of several cytokines and interleukins, promoting a systemic response to eradicate cancer (Leite de Oliveira and Bernards, 2018; Lee and Schmitt, 2019). Furthermore, even cells of progressed cancer can enter the senescent state (Lee and Schmitt, 2019). This can be induced by several rounds of chemotherapy treatment (Leite de Oliveira and Bernards, 2018). Although paradoxically, senescence also has shown to have pro-tumorigenic activity, especially in promoting cancer relapse following chemotherapy (Demaria et al., 2017).

Several mechanisms are used by cancerous cells to evade senescence activation and disrupt cell cycle arrest, promoting cell cycle progression. Inactivation of the $p27^{KIP1}$ is an important step of such mechanisms. There are mutations that favor the activation of proteins promoting the function of the CyclinE-CDK2 complex, phosphorylating $p27^{KIP1}$ and tagging it for degradation. This represses cyclin D, allowing cell cycle progression, favouring cancer cell proliferation (Hanahan and Weinberg, 2011). On the other hand, AKT, a serine/threonine kinase, can also inhibit $p27^{KIP1}$ and promote cell cycle progression. The activity of AKT can be upregulated directly by mutations causing overexpression of the AKT gene. AKT signalling can also be upregulated indirectly by mutations causing a decrease in the exogenous TGFβ stimulation or an increase in stimuli from exogenous mitogens. These changes in exogenous stimuli activate phosphatidylinositol 3-kinase

(PI3K), which activates AKT. AKT then acts by translocating $p21^{CIP1}$ and $p27^{KIP1}$ from the nucleus to the cytoplasm, where they are unable to inhibit the proteins that promote cell cycle progression (Hanahan and Weinberg, 2011).

A key characteristic of cancer cells is the deregulation of cell cycle checkpoint proteins such as the cyclin-dependent kinases (CDKs) CDK4 and CDK6 leading to uncontrolled cell proliferation. Molecular changes at CDKs level have been reported in various cancer types making them an attractive potential target for new treatments. CDK inhibitors, in particular CDK4/6 inhibitors (Abemaciclib, Palbociclib and Ribociclib), induce cell-cycle arrest and subsequent senescence in several cancer cell lines and mouse models (Asghar et al., 2015; Alvarez-Fernandez and Malumbres, 2020; Carpintero-Fernandez et al., 2022). Palbociclib is a drug for oestrogen-receptor-positive breast cancer (ER^+). ER^+ is the type of breast cancer where cancerous cells proliferate in response to oestrogen stimulation. Palbociclib acts by selectively inhibiting CDK4/6, leading to the accumulation of unphosphorylated Rb finally inducing cell cycle arrest (Clark et al., 2016). Palbociclib combined with letrozole or other aromatase inhibitors was approved for breast cancer treatment in 2015. Since then, Palbociclib has shown positive therapeutic outcomes in gastric cancer, melanoma, liposarcoma and hepatocellular carcinoma (Finn et al., 2015).

The fact that evasion of senescence is an important step for cancer development lead to the hypothesis that re-activating senescence in cancerous cells can reduce tumour progression. Thus, the discovery of drugs that can induce senescence in cancer cells can be a major contribution to the research field of cancer treatment. On the other hand, a great effort is currently ongoing to develop drugs that selectively eliminate senescent cells -senolytics. It has been shown that the use of senolytics in cancer prevents cancer progression in a variety of mouse models (Dolgin, 2020). Importantly, the group of Scott Lowe has recently developed a more specific technique to selectively eliminate senescent cells: via the generation of a Chimeric Antigen Receptor (CAR construct) targeting the urokinase-type plasminogen activator receptor (uPAR) which is expressed in senescent cells. Using this technology the authors where able to ablate senescent cells in mouse models of lung cancer and liver fibrosis (Amor et al., 2020).

CONTROVERSIES AND UNKNOWNS IN THE SENESCENCE FIELD

In spite of the huge scientific advances made in the last decades since the discovery of senescence in the early 1960s, there are still many open questions in the field. One example is the heterogeneity present upon the induction of senescence, where different cells are at different states in the activation of this phenotype. This added to the fact that a variety of specific but uncharacterized biomarkers can be induced makes it extremely difficult not only for their identification but also for their pharmacological targeting via senolytics and senomorphics (Hernandez-Segura et al., 2017). Additionally, evidence is building up that senescence is a stable, but not irreversible, cellular state. In fact, this novel characteristic of senescent cells has been attributed to the plasticity of their SASP in different contexts such as cancer, reprogramming and rejuvenation (Mosteiro et al., 2016; Ocampo et al., 2016; Ritschka et al., 2017; Rhinn et al., 2019; Fafian-Labora et al., 2020; Carpintero-Fernandez et al 2022). Importantly, recent evidences show that the SASP is not unique and static as initially thought but that it is dynamic, changing with time depending on trigger, context and cellular type (Hoare et al., 2016; Lee and Schmitt, 2019). The functions these variable SASP components have on their surroundings and specially on their interaction with the immune system is currently under thorough scrutiny.

CONCLUSION

In summary, the presence of senescent cells has been identified in numerous diseases related to ageing. In addition, their partial contribution to deleterious effects on the organism is starting to be well documented. Altogether, this brings light into the perspective that ageing and age-related diseases can be cured or at least delayed by human interventions. However, the fact that different cell types undergo senescence, that there is no single gold standard marker to identify senescence and that the markers of senescent cells most likely change depending on the microenvironment and with time makes therapeutic treatment very challenging. This in addition to the fact that the activation of senescence is beneficial in certain circumstances and for several pathologies. Thus, more research effort is required to deeply understand this complex cellular phenotype and how it influences the microenvironment, tissue and organism.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Association of intrinsic capacity with functional ability, sarcopenia and systemic inflammation in pre-frail older adults

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Background: Decline in intrinsic capacity (IC) has been shown to accelerate progression to disability. The study aims to explore association of IC composite score with functional ability, sarcopenia and systemic inflammation in pre-frail older adults.

Methods: Cross-sectional study of pre-frail older adults ≥60 years old recruited from the community and primary care centers. Composite scores of four domains of IC were measured: locomotion, vitality, cognition and psychological. FRAIL scale was used to define pre-frailty. Muscle mass was measured using the bioelectrical impedance analysis. Systemic inflammation biomarkers [Interleukin-6 (IL-6), Interleukin-10 (IL-10), Tumor Necrosis Factor Alpha (TNF-α), and Growth differentiated factor 15 (GDF-15)] were measured. Participants in the lowest tertile (T1) exhibited greater decline in IC.

Results: A total of 398 pre-frail older adults were recruited, mean age was 72.7 ± 5.8 years, 60.1% female, education level 7.8 years, and 85.2% were of Chinese ethnicity. A total of 75.1% had decline in locomotion, 40.5% in vitality, 53.2% in cognition and 41.7% in psychological domain. A total of 95% had decline in at least one domain. T1 was significantly associated with ADL impairment (aOR 3.36, 95% CI 1.78–6.32), IADL impairment (aOR 2.37, 95% CI 1.36–4.13), poor perceived health (aOR 0.96, 95% CI 0.95–0.98), fall (aOR 1.63, 95% CI 1.05–2.84), cognitive impairment (aOR 8.21, 95% CI 4.69–14.39), depression (aOR 101.82, 95% CI 33.62–308.37), and sarcopenia (aOR 2.40, 95% CI 1.60–5.45). T1 had significant associations with GDF-15, IL-10, and IL-10 to TNF-α ratio.

Conclusion: Decline in IC composite score among pre-frail older adults was associated with functional limitation, sarcopenia, and systemic inflammation.

KEYWORDS

intrinsic capacity, sarcopenia, systemic inflammation, pre-frail older adults, growth differentiation factor 15

Introduction

Population aging is a global phenomenon and by 2050, the number of older adults aged 65 years old and above will double to 1.5 billion (1). Aging is associated with decline in hearing, vision, mobility, and cognition, along with an increased prevalence of non-communicable diseases. These factors collectively contribute to the risk of frailty, dementia, disability, and mortality (2). Countries worldwide, including Singapore are adopting a population-wide approach to healthy aging prioritizing preventive health measures to mitigate long term health and social care cost (3). Functional ability encompasses both physical and cognitive ability, and is determined by the interaction of intrinsic capacity (IC) with environment (4). IC was first described in the World Report on Ageing and Health as a composite of physical, cognitive, psychological, vitality and sensory capacities. It is a paradigm shift from the usual disease-based approach to function and physiological reserve concept which has a better predictive ability for functional decline and incident disability (5, 6). The decline in IC can lead to increased socio-economic cost, participation restriction, frailty, disability, social isolation, and mortality (7, 8). In 2019, the World Health Organization published The Integrated Care for Older People (ICOPE) care pathway. This approach recommends screening for IC decline followed by person-centered assessment, personalized intervention, and monitoring plan (1, 4).

Frailty is a multi-dimensional dynamic construct caused by decline in physiological reserve which increases vulnerability to adverse outcomes when exposed to stressors (9). IC serves as an indirect measure of physiological reserve. Sarcopenia, defined as age related decline in muscle mass accompanied by reduced muscle strength, or physical performance is a component of physical frailty (10). It is increasingly recognized as a global health problem due to its association with morbidity, mortality and many chronic diseases such as fatty liver disease, dementia and diabetes mellitus (10–12). Notably, the co-existance of frailty with conditions such as liver fibrosis is associated twice the risk of overall mortality (13). Frailty, sarcopenia and IC decline can co-exist in the same individual accelerating the onset of disability (8, 14). Pre-frailty is a transition phase from robust to frailty with a prevalence rate ranging from 34.6 to 50.9% depending on the population studied and the frailty screening tools used (15). Liu et al demonstrated that 83.3% of pre-frail older adult have at least one IC impairment at baseline (16). Impairment in any of the IC domains in pre-frail older adults have shown to accelerate frailty progression (17–19).

Systemic inflammation is a well-known hallmark of aging and is associated with dementia, frailty, and sarcopenia (20). A systematic review reported significant association of plasma c-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor receptor-1 (TNFR-1) with frailty (20). In addition, Lu et al. (21) recently showed that lower baseline IC was associated with higher inflammatory biomarkers such as plasma CRP, IL-6, TNFR-1, and growth differentiation factor-15 (GDF-15) (21). GDF-15 is also known as macrophage inhibitory cytokine-1 and recognized as a biomarker for mitochondrial dysfunction. It is both a pro-inflammatory and anti-inflammatory cytokine where it exerts protective effect through immune-modulatory function and serves as a poor prognostic biomarker in myopathies, cancer, and cardiovascular disease (22). IL-10 is a potent anti-inflammatory cytokine and increases in response to inflammatory cascade (23). Besides its role in neurodegenerative diseases, low or absent IL-10 in mice has shown to be associated with frailty (24, 25).

While the concept and definition of IC has been accepted by most researchers globally, the measurement of IC remains an area of ongoing debate. There is yet no ideal measurement tools nor calculation models for IC composite scores. There is a suggestion that IC should be interpreted as a composite score and a system as the outcomes are determined by dynamical interrelations between domains which share common biological pathways (26). To date, there are limited studies on association of IC composite scores with functional ability, systemic inflammation, and sarcopenia in pre-frail older adults who are at highest risk of progressing to frailty and disability. There is only one recent study which reported association of IC with sarcopenia in hospitalized older person (14). The aim of this study is to explore association of IC composite score with functional ability, sarcopenia and systemic inflammation in pre-frail older adults.

Materials and methods

Study participants

This is a secondary cross-sectional analysis of baseline data from a multidomain intervention study in pre-frail older adults ≥60 years old recruited from the community and primary care centers in Singapore between February 2019 and May 2022 (27, 28). A total of 502 participants were recruited but complete demographic information and body composition analysis were available for 398 participants due to constraints of COVID-19 restrictions. Participants were screened for frailty using the FRAIL scale and pre-frailty was defined by a score of 1–2 out of a maximum score of 5 (29). The details on recruitment, biomarkers and interventions are described in earlier studies (27, 28). Recruited participants should be able to provide consent, follow instructions and ambulant. Exclusion criteria included nursing home residents, presence of pacemaker or defibrillator

and underlying psychiatric conditions. This study conformed to the principles of the Declaration of Helsinki and was approved by The National Healthcare Group Domain Specific Review Board (Reference: 2018/01183 and 2019/00017). Informed consent was obtained from all participants involved in the study.

Intrinsic capacity

Four domains of intrinsic capacity (IC) were evaluated–locomotion, vitality, cognition and psychological (**Supplementary Table 1**). Participants were given a score from 0 to 2 for each domain. Score of 0 or 1 indicates a decline and 2 no decline, with a total score of 8 (lower scores representing greater IC decline) (30). Locomotion was assessed using four meter gait speed and 5x sit-to-stand (5x STS) timing. The 5x STS timing was measured by the time taken to stand five times consecutively from a seated position without any arm support. Gait speed <1 m/s and/or 5x STS < 12 s were considered impaired locomotion (31). Vitality domain comprised of nutritional status and appendicular skeletal muscle index (ASMI). The Mini Nutritional Assessment-Short Form was used to evaluate nutritional status. With a maximum score of 14, <8 indicates malnourished and 8–11 at risk of malnutrition (32). Body composition was assessed using the InBody S10 multi-frequency bioelectrical impedance analyzer. InBody S10 provides results on segmental lean analysis and ASMI was calculated based on sum of lean mass of 4 limbs divided by height squared. Low ASMI was defined as <7.0 kg/m^2 for males and <5.7 kg/m^2 for females based on the Asia Working Group for Sarcopenia (AWGS) 2019 consensus criteria (31).

Cognition domain was evaluated using the Montreal Cognitive Assessment (MoCA) and self-reported subjective cognitive decline. With a maximum score of 30, participants scoring <26 were considered cognitively impaired (33). Subjective cognitive decline (SCD) was defined based on a question "do you feel that you have more problems with memory than most?" (34). Psychological domain was evaluated using the 15-item Geriatric Depression Scale (GDS-15), and a single question from the EuroQol-5 Dimensions (EQ-5D) question on anxiety/ depression. Depression was defined as GDS-15 score >5 (35). The EQ-5D question scoring ranged from 0 (not anxious/depressed), 1 (slight anxious/depressed) to 4 (extremely anxious/depressed) (34, 36). Scoring and distribution are summarized in **Supplementary Table 1**. Participants were then split into tertiles based on their total IC score.

Co-variates

Trained research assistants administered the study protocol gathering information on demographics, medications, chronic diseases, cognition, falls, sarcopenia, functional status, pain, and perceived health. Polypharmacy was defined as taking ≥5 medications daily and multimorbidity as ≥2 chronic diseases (hypertension, hyperlipidaemia, diabetes, heart disease, stroke, cancer, peripheral arterial disease, lung disease, kidney disease, osteoporosis). Perceived health was assessed using the EuroQoL Visual Analog Scale (36). Activities of daily living (ADL) was evaluated using Katz's ADL questionnaire with a maximum score of 6 and instrumental activities of daily living (IADL) using the Lawton and Brody's IADL questionnaire with a maximum score of 8 (37, 38). The Rapid Physical Assessment (RAPA) was used to assess physical activity (39).

Maximum handgrip strength (HGS) was measured in a seated position using the Jamar hand dynamometer on with elbow flexed at 90°. Low HGS was defined as <28 kg for males and <18 kg for females (31). The Short Physical Performance Battery (SPPB)–scored with a maximum of 12 points across three components–balance, gait and chair-stand was also administered. SPPB < 9 was considered poor performance (31). Four-meters gait speed was measured with 3 m of acceleration and deceleration path.

Muscle mass indices and sarcopenia

Readings for body cell mass (BCM), and appendicular skeletal mass (ASM) were obtained from InBody S10 multi-frequency bioelectrical impedance analyzer. Diagnosis of sarcopenia was based on the 2019 Asian Workgroup for Sarcopenia (AWGS) criteria (31).

Inflammatory biomarkers

GDF-15, IL-6, IL-10 and Tumor Necrosis Factor-Alpha (TNF-α) cytokines were measured by accredited hospital-based laboratory. Enzyme-linked immunosorbent Assay was used to measure GDF-15 with a detection range of 2.0–2400 pg./mL and IL-10 with a detection range of 2.0–400.0 pg./mL. IL-6 was measured using the electrochemiluminescence immunoassay (ECLIA) with a detection range between 1.5 and 50 000 pg./mL. Immunoenzymetric assay was used to measure TNF-α cytokine with a detection range between 1.0 and 498 pg/mL. The ratio of IL-10 to TNF-α was also calculated.

Statistical analysis

All analyses were conducted using SPSS 28.0. Statistical significance was set at a two-sided 5% level. Descriptive analyses for categorical and continuous variables were presented as frequencies with percentages and mean ± standard deviation, respectively. Univariate analysis for numerical measures across the groups was performed using the Welch test to account for unequal sample sizes, followed by Games-Howell *post-hoc* tests for pairwise comparisons. For categorical variables, we used Chi-Square and Fisher's Exact Test, with Bonferroni's correction. Baseline plasma biomarker levels were summarized as medians with interquartile range. We compared baseline values using Mood's median test.

Multinomial regression was conducted to investigate the association between IC and body composition, comparing it to participants with better IC in Tertile 3 (T3). We adjusted for age, gender, ethnicity, education years, and physical activity. Both unadjusted and adjusted odds ratios (ORs), along with their 95% confidence intervals (CIs), were reported. Additionally, we employed quantile regression to explore the relationship between IC and plasma biomarkers. Again, we provided unadjusted and adjusted β-coefficients, along with their 95% CIs.

Results

Participant characteristics and demographics

The decline in individual IC domain was 75.1% in locomotion, 40.5% in vitality, 53.2% in cognition and 41.7% in psychological domain (Figure 1). Amongst them, 95.0% had decline in at least one domain, 68.6% in two and 34.5% in three and 12.6% in all four domains (Supplementary Table 2). Of the 398 older adults, mean age was 72.7 ± 5.8 years, 60.1% female, education level 7.8 ± 4.4 years, and 85.2% were of Chinese ethnicity (Table 1). Amongst them, 34.2% were in Tertile 1 (T1), 22.1% in Tertile 2 (T2), and 43.7% in T3. Those in T3 were the youngest (71.0 ± 5.2 years), followed by T2 (73.0 ± 6.1 years), and T1 (74.3 ± 6.1 years). Participants in T1 had the lowest education level (6.4 ± 4.2 years) vs. T2 (8.1 ± 4.2 years) and T3 (8.8 ± 4.4 years). Perceived health rating was significantly lower in T1 (65.5 ± 15.6) compared with T3 (72.1 ± 13.8).

MoCA score was lowest in T1 (22.8 ± 5.2) followed by T2 (25.6 ± 4.0) and T3 (27.1 ± 2.6). The prevalence of malnutrition or at risk of malnutrition was 32.4% in T1, 15.9% in T2 and 8.6% in T3. Participants in T1 had the highest cognitive impairment rates (69.9% vs. 37.5% vs. 19.0%, respectively), depression rates (63.2% vs. 21.6% vs. 2.3%, respectively), at least 1 ADL (30.9% vs. 20.5% vs. 10.9%, respectively) and IADL impairments (41.9% vs. 21.6% vs. 19.0%, respectively).

The decline in locomotion domain was the most prevalent in T1 (93.4%) followed by T2 (83.0%) and T3 (56.9%). T3 compared to T2 and T1 participants had the fastest gait speed (1.1 ± 0.3 m/s vs. 0.9 ± 0.2 m/s vs. 0.8 ± 0.3 m/s), highest handgrip strength (23.2 ± 7.2 kg vs. 22.4 ± 6.2 kg vs. 19.1 ± 6.4 kg), shortest 5x sit-to-stand timing (11.2 ± 3.2 s vs. 13.8 ± 3.6 s vs. 15.4 ± 6.3 s) and highest SPPB performance (10.7 ± 1.6 vs. 9.5 ± 1.8 vs. 8.4 ± 2.4). T1 had the highest proportion of participants with slow gait speed (83.8% vs. 67.0% vs. 36.8%), low handgrip strength (67.6% vs. 47.7% vs. 47.1%), longer 5x STS timing (69.1% vs. 61.4% vs. 32.8%), and highest rates of poor SPPB performance (48.5% vs. 23.9% vs. 8.6%).

Association of intrinsic capacity composite score with functional ability

For T1 compared with T3, IC composite score was significantly associated with at least 1 ADL impairment (aOR 3.36, 95% CI 1.78 to 6.32), IADL impairment (aOR 2.37, 95% CI 1.36 to 4.13), poor perceived health (aOR 0.96, 95% CI 0.95 to 0.98), at least 1 fall in the past year (aOR 1.63, 95% CI 1.05 to 2.84), cognitive impairment (aOR 8.21, 95% CI 4.69 to 14.39), and depression (aOR 101.82, 95% CI 33.62 to 308.37) (Table 2). For T2, only cognitive impairment (aOR 2.36, 95% CI 1.30 to 4.27), and depression (OR 12.97, 95% CI 4.20 to 40.00) had significant association.

Intrinsic capacity and sarcopenia

T1 participants had the lowest ASMI (6.5 ± 2.4 kg/m^2 vs. 7.7 ± 3.3 kg/m^2 vs. 7.2 ± 1.6 kg/m^2), BCM (22.8 ± 6.3 kg vs. 26.5 ± 9.4 kg vs. 27.7 ± 6.1 kg) and highest prevalence of sarcopenia (23.5% vs. 17.0% vs. 5.7%). T1 was significantly associated with ASMI (aOR 0.78, 95% CI 0.62 to 0.96), BCM (aOR 0.85, 95% CI 0.79 to 0.91), and sarcopenia (aOR 2.40, 95% CI 1.60 to 5.45). T2 was significantly associated with BCM (aOR 0.91, 95% CI 0.85 to 0.97), and sarcopenia (aOR 2.38, 95% CI 1.07 to 5.89) (Table 2).

Association of intrinsic capacity composite score with systemic inflammatory biomarkers

Serum GDF-15 was significantly elevated in T1 participants (Table 3). T1 had significant associations with GDF-15 (β 263.14, 95% CI 105.36 to 541.64), IL-10 (β −0.73, 95% CI −1.24 to −0.21), and IL-10 to TNF-α ratio (β −107.58, 95% CI −182.08 to −33.07). T2 also had significant associations with IL-10 (β −0.47, 95% CI −0.98 to −0.03) and IL-10 to TNF-α ratio (β −95.74, 95% CI −166.56 to −24.91) (Table 4).

Discussion

This study represents one of the first few investigations into the prevalence of IC decline and its association with functional ability, sarcopenia, and systemic inflammation in pre-frail older adults. Participants in the highest tertile were significantly younger, better educated, and had higher cognitive scores. They also exhibited lower rates of depression, functional impairment, and malnutrition. Higher IC composite scores have shown to be associated with reduced frailty and disability progression (40). Our findings revealed that 95% of pre-frail older adults experienced at least one IC domain decline, slightly surpassing the 89.9% prevalence observed in participants with sarcopenia and the 83.3% prevalence in pre-frail older adults from China at baseline (14, 16). Notably, the proportion of pre-frail older adults with declines in individual IC domains was nearly triple that of the original ICOPE Pilot validation study in China: 75.1% compared to 25.3% in locomotion, 40.5% compared to 16.2% in vitality, 53.2% compared to 46.8% in cognition, and 41.7% compared to 12.0% in the psychological domain (41). This could be attributed to different population group where the participants from the ICOPE Pilot validation study were from hospitalized cohort, had a lower mean age, and were evaluated using simplified measurement tools such as 5x-STS for mobility and 3-item recall and orientation for cognitive decline. Given the significant heterogeneity in measurement of individual domains, there has been a recent collection of publication in collaboration with the WHO on standardizing healthy aging assessments (42).

Locomotor impairment was prevalent across all tertiles, with 93% of participants in T1 and 56.9% in T3 exhibited low gait speed or 5x-STS. In a 2-year longitudinal study, new impairment in locomotion and vitality were associated with progression from non-frail to frail status (16). Another study reported that impaired locomotion and vitality at baseline were associated with "kept frail" or "worsened frailty status" (6). While the domains are separate entities and interventions may be domain specific, there are significant interactions between domains and

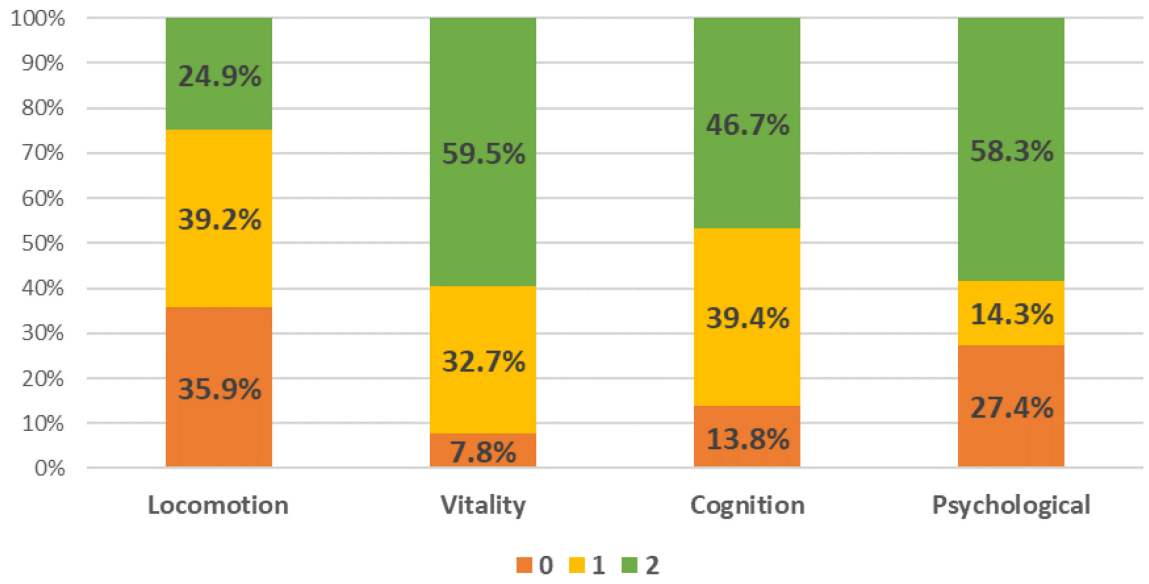

FIGURE 1
Distribution of individual intrinsic capacity domain score.

decline in one can impact decline in another with cumulative impact on functional ability (8, 43). Our study demonstrated this interplay: participants in T1 were three times more likely to have cognitive impairment, eight times more likely to have a decline in psychological domain and four times more likely to be sarcopenic.

Functional ability is one of the key measurement of the success of the Decade of Healthy Aging action plan which was declared by the United Nation (1, 4). Lower composite scores were significantly associated with functional and cognitive impairment, depression, poor perceived health and falls. Stolz et al. (12) showed significant heterogeneity in IC decline over 21 years where 1 point decline was associated with 7% increase in risk of ADL disability, 6% increase in nursing home admission and 5% increased risk of mortality (12). Studies have reported significant variability in domains which may predict adverse outcomes in different populations. In the Multidomain Alzheimer Preventive Trial (MAPT) cohort, mobility decline, depression and visual impairment were associated with higher incidence of frailty over 5 years, and each additional decline in IC was associated with higher incidence frailty by 47%, IADL decline by 27%, and ADL decline by 23% (8). Yu et al. (44) reported that cognitive decline, limited mobility, visual impairment and depression predicted incident disability whereas cognitive decline and limited mobility predicted emergency department visits amongst Chinese community dwelling older adults over 1 year (44). On the other hand, low nutrition scores and low balance performance predicted 3-year mortality and falls in nursing home residents in Belgian (45).

Lower tertiles of IC composite score were significantly associated with sarcopenia and muscle mass indices such as body cell mass and appendicular skeletal muscle mass. Sarcopenia has shown to be associated with individual IC domains such as hearing, depression, dementia, functional mobility, and vision (11, 46, 47). Notably, only one study has explored the association between IC composite score and sarcopenia but in hospitalized older adults whereas our study population were community dwelling older adults (14).

Despite the growing interest in IC, limited research has explored its associations with systemic inflammation. In this study, we examine the link between IC composite scores and specific biomarkers. Lowest tertile of IC composite score demonstrated significant associations with high GDF-15, low IL-10, and IL-10 to TNF-α ratio. Secondary analysis from the MAPT study with longitudinal follow up over 60 months revealed that rapid decline in IC trajectory correlated with TNFR-1, GDF-15, and monocyte chemoattractant protein-1 (21). Our results are in keeping with other studies which showed significant relationship of GDF-15 with sarcopenia, frailty, gait speed and poor physical function in older adults (48). A prior systematic review did not show association of IL-10 with frailty possibly due to limited data as only nine studies were included on IL-10 in and frailty (20). Interestingly, IL-10 knockout mice exhibited increased expression of serum IL-6, and faster muscle strength decline (24). TNF-α/IL-10 ratio serves as a surrogate for immune homeostasis which measures ratio of pro- and anti-inflammatory cytokines. Prior studies have shown that high TNF-α/IL-10 ratio have been associated with frailty, motoric cognitive risk syndrome, severity of burn injury and susceptibility to infections in burn patients (25, 49). TNF-α and IL-6 did not significantly differ between groups, possibly due to enrolled participants being pre-frail (20). In addition, prior studies reported significant association of frailty and IC with TNFR-1 which is widely expressed and implicated in cell death, and inflammation (50).

Our study further strengthens the concept of multidimensional nature of IC in pre-frail older adults and the impact of composite score on functional ability and systemic inflammation. However, there are several limitations which warrant mention. First and foremost, there is no gold standard for diagnosis of sarcopenia.

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TABLE 1 Baseline characteristics.

	Overall n = 398	Tertile 1 n = 136 (34.2%)	Tertile 2 n = 88 (22.1%)	Tertile 3 n = 174 (43.7%)	P-value
Demographics					
Age, years (range)	72.70 (60–91)	74.26 (63–91)	72.95 (61–91)	71.36 9 (60–85)	<**0.001**
Gender					0.076
Male	159 (39.9)	44 (32.4)	37 (42.0)	78 (44.8)	
Female	239 (60.1)	92 (67.6)	51 (58.0)	96 (55.2)	
Ethnicity					0.737
Chinese	339 (85.2)	113 (83.1)	75 (85.2)	151 (86.8)	
Malay	25 (6.3)	11 (8.1)	7 (8.0)	7 (4.0)	
Indian	31 (7.8)	11 (8.1)	5 (5.7)	15 (8.6)	
Others	3 (0.8)	1 (0.7)	1 (1.1)	1 (0.6)	
BMI, kg/m^2	25.44 ± 4.64	24.80 ± 5.21	25.47 ± 4.71	25.92 ± 4.08	0.106
Education, years	7.83 ± 4.38	6.44 ± 4.15	8.11 ± 4.22	8.76 ± 4.39	<**0.001**
Chronic disease					
Hypertension	270 (67.8)	94 (69.1)	59 (67.0)	117 (67.2)	0.834
Hyperlipidaemia	300 (75.4)	102 (75.0)	68 (77.3)	130 (74.7)	0.901
Diabetes	184 (46.2)	67 (49.3)	37 (42.0)	80 (46.0)	0.569
Multi-morbidity	307 (77.1)	107 (78.7)	68 (77.3)	132 (75.9)	0.842
Polypharmacy	112 (28.1)	38 (27.9)	23 (26.1)	51 (29.3)	0.865
Perceived health rating	69.39 ± 14.34	65.50 ± 15.55	69.73 ± 12.23	72.14 ± 13.77	<**0.001**
RAPA total	3.25 ± 1.56	2.92 ± 1.43	3.22 ± 1.61	3.52 ± 1.59	**0.003**
MoCA total	25.28 ± 4.41	22.79 ± 5.22	25.61 ± 4.04	27.06 ± 2.63	<**0.001**
≥1 Fall in 12 months	103 (25.9)	46 (33.8)	18 (20.5)	39 (22.4)	**0.032**
Depression	109 (27.4)	86 (63.2)	19 (21.6)	4 (2.3)	<**0.001**
Subjective cognitive decline	106 (26.6)	60 (44.1)	26 (29.5)	20 (11.5)	<**0.001**
≥1 ADL impairment	79 (19.8)	42 (30.9)	18 (20.5)	19 (10.9)	<**0.001**
≥1 IADL impairment	109 (27.4)	57 (41.9)	19 (21.6)	33 (19.0)	< **0.001**
Nutrition status					<**0.001**
Malnourished	2 (0.5)	2 (1.5)	0 (0.0)	0 (0.0)	
At risk	71 (17.8)	42 (30.9)	14 (15.9)	15 (8.6)	
Normal	325 (81.7)	92 (67.6)	74 (84.1)	159 (91.4)	
IC total	5.05 ± 1.74	3.05 ± 1.03	5.00 ± 0.00	6.63 ± 0.68	<**0.001**
IC domain decline					
Locomotion	299 (75.1)	125 (93.4)	73 (83.0)	99 (56.9)	<**0.001**
Vitality	161 (40.5)	93 (68.4)	31 (35.2)	37 (21.3)	<**0.001**
Cognition	212 (53.2)	111 (81.6)	52 (59.1)	49 (28.2)	<**0.001**
Psychological	166 (41.7)	111 (81.6)	37 (42.0)	18 (10.3)	<**0.001**
Physical performance					
Max gait speed, m/s	0.95 ± 0.30	0.81 ± 0.28	0.93 ± 0.24	1.08 ± 0.28	<**0.001**
Slow gait speed	237 (59.5)	114 (83.8)	59 (67.0)	64 (36.8)	<**0.001**
Max handgrip strength, kg	21.67 ± 6.93	19.09 ± 6.35	22.38 ± 6.16	23.32 ± 7.17	<**0.001**
Low handgrip strength[1]	216 (54.3)	92 (67.6)	42 (47.7)	82 (47.1)	**0.002**

(Continued)

TABLE 1 (Continued)

	Overall n = 398	Tertile 1 n = 136 (34.2%)	Tertile 2 n = 88 (22.1%)	Tertile 3 n = 174 (43.7%)	P-value
5x STS time (s)	13.17 ± 4.91	15.38 ± 6.34	13.75 ± 3.60	11.19 ± 3.18	<**0.001**
Poor 5x STS	205 (51.5)	94 (69.1)	54 (61.4)	57 (32.8)	<**0.001**
SPPB, total	9.66 ± 2.22	8.37 ± 2.41	9.51 ± 1.79	10.74 ± 1.62	<**0.001**
Poor SPPB	102 (25.6)	66 (48.5)	21 (23.9)	15 (8.6)	<**0.001**
Body composition					
ASMI, kg/m^2	7.05 ± 2.36	6.46 ± 2.38	7.74 ± 3.32	7.19 ± 1.63	<**0.001**
Body cell mass, kg	25.81 ± 7.23	22.82 ± 6.31	26.47 ± 9.42	27.71 ± 6.05	<**0.001**
Whole body phase angle	5.48 ± 2.62	5.15 ± 2.48	6.08 ± 3.41	5.46 ± 2.27	0.146
Sarcopenia (AWGS)[2]	57 (14.3)	32 (23.5)	15 (17.0)	10 (5.7)	**0.007**

Values presented as n (%) or mean ± SD. BMI, body mass index; RAPA: rapid assessment of physical activity; MoCA, Montreal cognitive assessment; ADL, activities of daily living; IADL, instrumental activities of daily living; MNA, mini nutritional assessment; IC, intrinsic capacity; SPPB, short physical performance battery rest; STS, sit-to-stand; ASMI, appendicular skeletal muscle index; AWGS, Asian working group for sarcopenia.
[1] Adjusted for gender.
[2] Based on Asian Working Group for Sarcopenia (AWGS) 2019's definition. Values shown in bold indicate statistical significance.

TABLE 2 Association of intrinsic capacity composite score with functional ability and sarcopenia (Tertile 3 as reference).

	Tertile 1		Tertile 2	
	Unadjusted	Adjusted[#]	Unadjusted	Adjusted[#]
ADL impairment	**3.65 (2.00 to 6.64)**	**3.36 (1.78 to 6.32)**	**2.10 (1.04 to 4.24)**	1.91 (0.93 to 3.89)
IADL impairment	**3.08 (1.85 to 5.13)**	**2.37 (1.36 to 4.13)**	**1.18 (0.62 to 2.22)**	0.99 (0.51 to 1.91)
Perceived health	**0.97 (0.95 to 0.98)**	**0.96 (0.95 to 0.98)**	0.99 (0.97 to 1.01)	0.99 (0.97 to 1.01)
Cognitive impairment	**9.90 (5.85 to 16.77)**	**8.21 (4.69 to 14.39)**	**2.56 (1.44 to 4.55)**	**2.36 (1.30 to 4.27)**
Depression	**73.10 (25.56 to 209.09)**	**101.82 (33.62 to 308.37)**	**11.70 (3.84 to 35.65)**	**12.97 (4.20 to 40.00)**
Falls ≥ 1	**1.77 (1.07 to 2.93)**	**1.63 (1.05 to 2.84)**	0.89 (0.48 to 1.67)	0.88 (0.47 to 1.67)
ASMI	**0.73 (0.60 to 0.88)**	**0.78 (0.62 to 0.96)**	1.01 (0.92 to 1.11)	0.99 (0.89 to 1.12)
Body cell mass	**0.88 (0.83 to 0.92)**	**0.89 (0.84 to 0.95)**	**0.94 (0.90 to 0.99)**	**0.91 (0.85 to 0.97)**
Sarcopenia	**3.24 (1.50 to 6.97)**	**2.40 (1.06 to 5.45)**	**2.73 (1.14 to 6.53)**	**2.38 (1.07 to 5.89)**

Reference group: Tertile 3; Values presented as Odds Ratio (95% Confidence Interval).
Bold indicates significance ($p < 0.05$).
As defined by Asian Working Group for Sarcopenia 2019.
ASMI, appendicular skeletal muscle index.
[#] Adjusted for age, gender, ethnicity, education years and physical activity.

TABLE 3 Baseline plasma biomarker levels.

	Overall n = 107	Tertile 1 n = 39 (36.4%)	Tertile 2 n = 24 (22.4%)	Tertile 3 n = 44 (41.1%)	P-value
GDF-15 (pg/mL)	876.10 (679.40)	1183.95 (1112.60)[a]	1051.40 (721.20)	692.80 (476.40)[a]	**0.030**
IL-6 (pg/mL)	2.70 (1.40)	2.85 (1.90)	2.80 (1.40)	2.70 (1.20)	0.883
IL-10 (ng/mL)	2.39 (1.32)	2.42 (1.33)	2.05 (1.42)	2.54 (1.44)	0.265
TNF-α (pg/mL)	7.50 (3.60)	8.40 (2.90)	7.80 (4.20)	6.90 (3.00)	0.116
IL-10 / TNF-α	311.48 (181.11)	276.50 (196.08)	291.15 (177.72)	346.47 (186.08)	0.088

Values presented as median (interquartile range).
[a] Values with common superscript alphabet are significantly different.
GDF-15: Growth Differentiation Factor-15. Bold indicates significance ($p < 0.05$). Data available for 107 participants.

Muscle mass measurement was made using the multi-frequency bioelectrical impedance analyzer which includes intramuscular fat, fibrotic and connective tissue. The D3 Creatine dilution method better predicts muscle mass and associated with functional status (51). Second, we lack information on the surrounding environment which can impact IC, participation restriction, hearing, and vision. These factors may impact other domains and overall scores. However, Liu et al reported that newly impaired locomotion and vitality were significantly associated with frailty progression (16). Both vision and hearing impairment have been shown to be

TABLE 4 Univariate and multiple adjusted quantile regression for plasma biomarkers (Tertile 3 as reference).

	Tertile 1		Tertile 2	
	Unadjusted	Adjusted[#]	Unadjusted	Adjusted[#]
GDF-15	**480.00 (214.47 to 745.53)**	**263.14 (105.36 to 541.64)**	338.80 (−57.05 to 620.55)	170.89 (−93.84 to 435.62)
IL-6	0.10 (−0.48 to 0.68)	0.04 (−0.39 to 0.47)	0.10 (−0.52 to 0.72)	0.02 (−0.39 to 0.43)
IL-10	−0.08 (−0.64 to 0.48)	**−0.73 (−1.24 to−0.21)**	−0.49 (−1.09 to 0.11)	**−0.47 (−0.98 to−0.03)**
TNF-α	1.60 (−0.75 to 3.13)	0.83 (−0.38 to 2.03)	1.80 (−0.18 to 3.42)	0.61 (−0.54 to 1.75)
IL-10 / TNF-α	−67.16 (−154.55 to 20.23)	**−107.58 (−182.08 to−33.07)**	−45.08 (−137.81 to 47.65)	**−95.74 (−166.56 to−24.91)**

Reference group: Tertile 3.
Values presented as β (95% Confidence Interval).
Bold indicates significance ($p < 0.05$).
GDF-15: Growth Differentiation Factor-15.
[#]Adjusted for age, gender, ethnicity, education years, polypharmacy, physical activity, falls and IADL impairment.

associated with sarcopenia. Third, the cross-sectional nature of the study limits causal association. Fourth, our study population were pre-frail limiting generalizability to the broader population. Fifth, the data on chronic disease, falls, function, and medications were based on self-report and maybe subject to recall bias. Sixth, as our study participants were ambulant and able to follow instructions, the association of IC with functional ability maybe under-reported. Seventh, sarcopenia diagnosis was made based on the Asian Working Group for Sarcopenia 2019 Consensus which recommended using the 6-meter walk; we used the 4-meter walk with a 3-meter of acceleration and deceleration path. It is known that multiple factors can affect gait speed such as distance, flooring surface, automatic vs. manual timing, clinical condition, endurance and starting test procedures. A systematic review reported a non-clinically significance median difference of 0.04 m/s between longer and shorter distance (52). Lastly, while SCD is recognized as a cognitive testing instrument, reporting of SCD may vary between different population and ethnic groups (40, 53).

It is becoming increasingly evident that both composite and individual domain scores are important in planning personalized interventions and measuring outcomes. Functional ability is determined by the inter-relationship between different IC domains where composite scores may be valuable in measuring impact of multidomain interventions or the impact of the Decade of Healthy Ageing action plans on quality of life, physical function, cognition, and mental health. Emerging studies show that baseline IC and inflammation better predict the onset of disability (21). In clinical practice, IC composite scores may be able to stratify surgical risk, guide medical treatment and rehabilitation strategies. However there are limited scientific publications in this field (42). Many countries are implementing public health program like the INSPIRE integrated care for older people (ICOPE)-CARE programme in Occitanic for screening of IC with personalized management (54). However, there are significant gaps which needs to be addressed such as validated screening tools for individual domains before routine screening at population level can be implemented. One such example is vitality where studies have used measures such as HGS, weight loss, fatigue, and nutrition. In addition, the association with functional ability and biomarkers need to be validated in longitudinal studies. Nonetheless, IC composite scores could potentially serve as a measure of biological aging.

Conclusion

The IC domains composite score was significantly associated with functional ability, perceived health, sarcopenia, and systemic inflammation biomarkers such GDF-15, IL-10, and IL-10/TNF-α ratio in pre-frail older adults. Future prospective longitudinal population studies are needed to validate association of sarcopenia and functional ability with IC composite scores.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the National Healthcare Group Domain Specific Review Board (Reference 2018/01183 and 2019/00017). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

RM: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project

administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review and editing. YC: Data curation, Formal Analysis, Writing – original draft, Writing – review and editing. DA: Formal Analysis, Writing – original draft, Writing – review and editing. BV: Supervision, Visualization, Writing – original draft, Writing – review and editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2024.1374197/full#supplementary-material

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Relationship between the severity of pre-frailty and the degree of adaptation of Ninjin'yoeito (NYT) on pre-frailty

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With the global trend towards longer life expectancies, there's an increasing emphasis on not just living longer, but also maintaining health and wellbeing into older age. This study explores the efficacy of Ninjin'yoeito (NYT) in the early stages of frailty, a critical period for preventive interventions. Taking account of the knowledge gap regarding the association between early frailty and NYT, we use data from workplace health checkups to examine the relationship between pre-frailty severity and NYT adaption. The objective of our research is to enhance the comprehension of early treatments using NYT to prevent the progression of frailty. A total of 314 employees of the Kyoto Industrial Health Association who received workplace health checkups between November 2021 and March 2023 and consented to this study were included in the analysis. Information on gender, age, body mass index (BMI), NYT-specific symptoms assessment, the Japanese version of the General Health Questionnaire-12 (GHQ-12), and the Kihon Checklist (KCL) were obtained. The correlation analysis revealed that there was a strong positive correlation between the number of applicable NYT indications and the GHQ-12 score ($r = 0.5992$, $p < 0.0001$). Similarly, a moderate positive correlation was observed between the number of applicable NYT indications and the KCL score ($r = 0.5030$, $p < 0.0001$). In the multivariate analysis, both GHQ-12 ($\beta = 0.49$, SE = 0.06, $t = 7.66$, 95% CI: 0.36 to 0.62, $p = 0.000$) and KCL ($\beta = 0.54$, SE = 0.12, $t = 4.29$, 95% CI: 0.29 to 0.79, $p = 0.000$) showed significant positive associations with the variance in the number of applicable NYT indications, indicating that

higher scores on these measures were related to a greater number of indications. NYT has the potential to be utilized not only as a therapeutic intervention for frailty, but also as a preventive measure.

KEYWORDS

frailty, Ninjin'yoeito (NYT), Revised Japanese version of the cardiovascular health study (revised J-CHS), Kihon checklist (KCL), general health questionnaire 12 (GHQ12)

Highlights

- This is the first study to investigate the relationship between the severity of frailty and the degree of adaption to Ninjin'yoeito (NYT) in employees who have underwent a workplace health checkup.
- A number of recent articles have documented the effectiveness of NYT in addressing frailty.
- We selected NYT-specific symptoms assessment, the Japanese version of the General Health Questionnaire-12 (GHQ-12), and the Kihon Checklist (KCL) to conduct our investigation.

Introduction

Advances in modern medicine since the 1950s have contributed significantly to extending human life expectancy, leading to a significant increase in the number and proportion of the elderly in the world population (Rau et al., 2008). A recent United Nations report underscores this demographic shift, projecting that the number of people aged 65 and over will more than double from 727 million in 2020 to more than 1.5 billion by 2050 (United Nations, 2023). This demographic trend underscores the importance of extending "healthy life expectancy. Healthy life expectancy is the period during which an individual can maintain daily life without health constraints. Addressing this will require not only medical advances, but also preventive measures to ensure that individuals can lead active and healthy lives into old age, thereby reducing healthcare costs and increasing overall wellbeing.

Frailty has emerged as a major obstacle in maintaining the health and extending the healthy life expectancy of elderly individuals. Frailty is a condition characterized by heightened physiological fragility, which has been linked to elevated chances of adverse health outcomes such as morbidity, falls, hospitalization, long-term care, institutionalization, and mortality. These consequences impose significant demands on healthcare and social systems (Clegg et al., 2013; Chen et al., 2014; Cesari et al., 2016). The worldwide population of aged individuals is steadily rising, leading to an increased recognition of the need of preventing and delaying the onset of frailty (Cesari et al., 2016; Puts et al., 2017).

The primary objective of the major statutory health checkup and advice programs in Japan is to mitigate the risk of lifestyle diseases by encouraging the adoption of healthy habits through health monitoring initiatives (Higa et al., 2021). In Japan, it is well acknowledged that the mere provision of checkup results to individuals is inadequate in eliciting behavioral modifications. These programs mandate companies to give health screenings for their employees, as well as further support like as medical consultations and health counseling, in cases where the checkup findings indicate a need for such assistance. In other words, the workplace health checkups conducted in Japan allow to get a comprehensive set of health-related information pertaining to employees, collected concurrently.

Ninjin'yoeito (NYT), a conventional Japanese Kampo medicine, is designed for individuals with a weakened constitution due to aging, illness recovery, diminished appetite, cold extremities, anemia, and nocturnal sweating (Uto et al., 2018). Containing twelve potent herbs such as ginseng, Japanese angelica root, peony root, rehmannia root, atractylodes rhizome, poria sclerotium, cinnamon bark, astragalus root, citrus Unshiu peel, polygala root, schisandra fruit, and glycyrrhiza, NYT is noted for its broad-spectrum efficacy in revitalizing the body's constitution, alleviating fatigue, malaise, anorexia, insomnia, and bolstering physical strength post-recovery (Miyano et al., 2018; Uto et al., 2018; Suzuki et al., 2019; Takayama et al., 2019; Hirai et al., 2020). Its application in modern clinical settings, particularly for frailty management in gastrointestinal, respiratory, and urinary functions, demonstrates its adaptability and relevance in contemporary healthcare. The effectiveness of NYT in addressing frailty has been documented in recent articles (Miyano et al., 2018; Uto et al., 2018; Suzuki et al., 2019; Takayama et al., 2019; Hirai et al., 2020), with an increasing understanding of its underlying mechanisms (Zhang et al., 2021; Amitani et al., 2022), though these are still under active investigation. This study aims to explore the relationship between frailty severity and the adaptation to NYT, utilizing data from workplace health checkups to deepen our understanding of its therapeutic potential and the applicability of NYT indications to prevent the progression of frailty.

Materials and methods

Study design and participants

This research is a multi-institutional collaboration between the Department of Kampo Pharmacology, Graduate School of Medical and Dental Sciences, Kagoshima University, Kyoto Industrial Health Association Foundation, and Gene Quest Co. The study was approved by the Ethical Review Committee of Kagoshima University with the committee's reference number 210176 (G449) and the Ethical Review Committee of Kyoto Industrial Health Association (approval number: S19-0008-02). Employees of the Kyoto Industrial Health Association who received workplace health checkups between November 2021 and March 2023 and consented to this study were included in the analysis.

TABLE 1 NYT-specific symptoms assessment.

Question	Score
Physical weakness: How many days in the past week did you feel?	0–7 (days)
General fatigue: How many days in the past week did you feel?	0–7 (days)
Loss of appetite: How many days in the past week did you feel?	0–7 (days)
Night sweats: How many days in the past week did you feel?	0–7 (days)
Coldness: How many days in the past week did you feel?	0–7 (days)
Anemia: How many days in the past week did you feel?	0–7 (days)
Total	0–42

NYT: Ninjin'yoeito

Data collection

Information on gender, age, body mass index (BMI), NYT-specific symptoms assessment, the Japanese version of the General Health Questionnaire-12 (GHQ-12), and the Kihon Checklist (KCL) were obtained.

In this study, we used a questionnaire specifically designed to assess indications for NYT, as shown in Table 1. Participants reported their experience during the past week of six main symptoms: loss of energy, general malaise, anorexia, night sweats, cold hands and feet, and anemia. Participants recorded the presence or absence of these symptoms daily using a scale from 0 (days without symptoms) to 7 (symptoms present daily). For the analysis, these daily reports were tabulated to produce an individual score of 0–7 for each symptom and a cumulative score across all symptoms. This comprehensive scoring system allowed for a nuanced assessment of the extent to which participants' experiences matched NYT-adaptive symptoms and provided a basis for analyzing the correlation between the severity of frailty and NYT-adaptability based on self-reported health indicators.

In response to the questions regarding the assessment of anemia, this questionnaire was designed to capture subjective experiences of anemia-related symptoms rather than clinical diagnoses. Participants were asked to reflect on their experiences over the past week and report the number of days they experienced anemia-related symptoms. This approach was intended to measure subjective perceptions of anemia-related symptoms and their impact on daily life, consistent with the holistic assessment principles of Kampo medicine. This self-reported questionnaire was part of a broader set of indicators used to understand potential indications for NYT and was not intended as a stand-alone diagnostic tool for anemia.

The GHQ-12 questionnaire is a widely used tool for screening psychological distress and mental health (Goldberg and Williams, 1988). It consists of 12 questions that assess an individual's recent experiences and feelings. Each question typically offers response options, such as "more than usual" or "less than usual," allowing individuals to indicate their level of agreement or disagreement. Each item assesses the severity of a mental problem over the past few weeks using a 4-point Likert-type scale (from 1 to 4). The score was used to generate a total score ranging from 0 to 48. The total score provides an indication of psychological wellbeing, with higher scores suggesting higher levels of distress. The validity and reliability of the GHQ-12 have been extensively investigated and confirmed in studies, including that conducted in 15 centers worldwide (Goldberg et al., 1997). Previous studies suggest that adolescents interpret the GHQ-12 in a manner similar to adults (Banks, 1983; Tait et al., 2003; Baksheev et al., 2011). The validity and reliability of the Japanese version of the GHQ-12 have been confirmed in adolescents (Nakagawa, 1982). The total score of GHQ-12 was used for the analysis.

The Kihon Checklist (KCL) is a concise and precise tool developed by the Ministry of Health Labor and Welfare in Japan used to assess the functional decline and frailty in older adults (Satake et al., 2016). It consists of 25 questions covering various domains, including physical strength, nutrition, oral health, social relationships, and cognitive function. Each question is answered with either a "yes" or "no" response. The total score ranges from 0 to 25, with a higher score indicating a higher level of frailty or functional decline (Satake et al., 2016). Total KCL scores were used in the analysis. In addition, according to the total score, the patients were divided into three groups according to the cutoff values: frail, pre-frail, and robust (Satake et al., 2016).

Statistical analysis

All statistical analyses were used by Stata version 16 (StataCorp LLC, College Station, TX, USA) and GraphPad Prism version 9.5.1 for MacOS (GraphPad Software, San Diego, CA, USA). The threshold of significance was set at 0.05. Descriptive statistics were calculated for all variables included in the study. We tested for normality using the Shapiro-Wilk test. Correlation analysis was performed to examine the relationships between the number of applicable NYT indications and the GHQ-12 score and between the number of applicable NYT indications and the KCL score. Spearman r was calculated to determine the strength and direction of the associations. A one-way analysis of variance was performed from the KCL score on the comparison of the number of

TABLE 2 Participants' characteristics: results expressed as median [interquartile range] or count (percentage).

	Total (n = 314)	Male (n = 126)	Female (n = 188)
Age (years)	47.0 [41.7–54.0]	52.0 [43.7–58.0]	46.0 [41.0–50.0]
BMI (kg/m^2)	22.0 [19.7–24.2]	22.3 [21.9–22.6]	20.7 [18.9–22.8]
Number of NYT applicable	4 [1–10]	3 [0–7.2]	6 [1–12]
GHQ-12	25.0 [22.0–29.0]	25.0 [21.0–30.0]	25.0 [23.0–29.0]
KCL	6 [5–8]	7 [5–9]	6 [4–8]

Abbreviations:BMI: body mass index; NYT: Ninjin'yoeito; GHQ: general health questionnaire; KCL: kihon check list.

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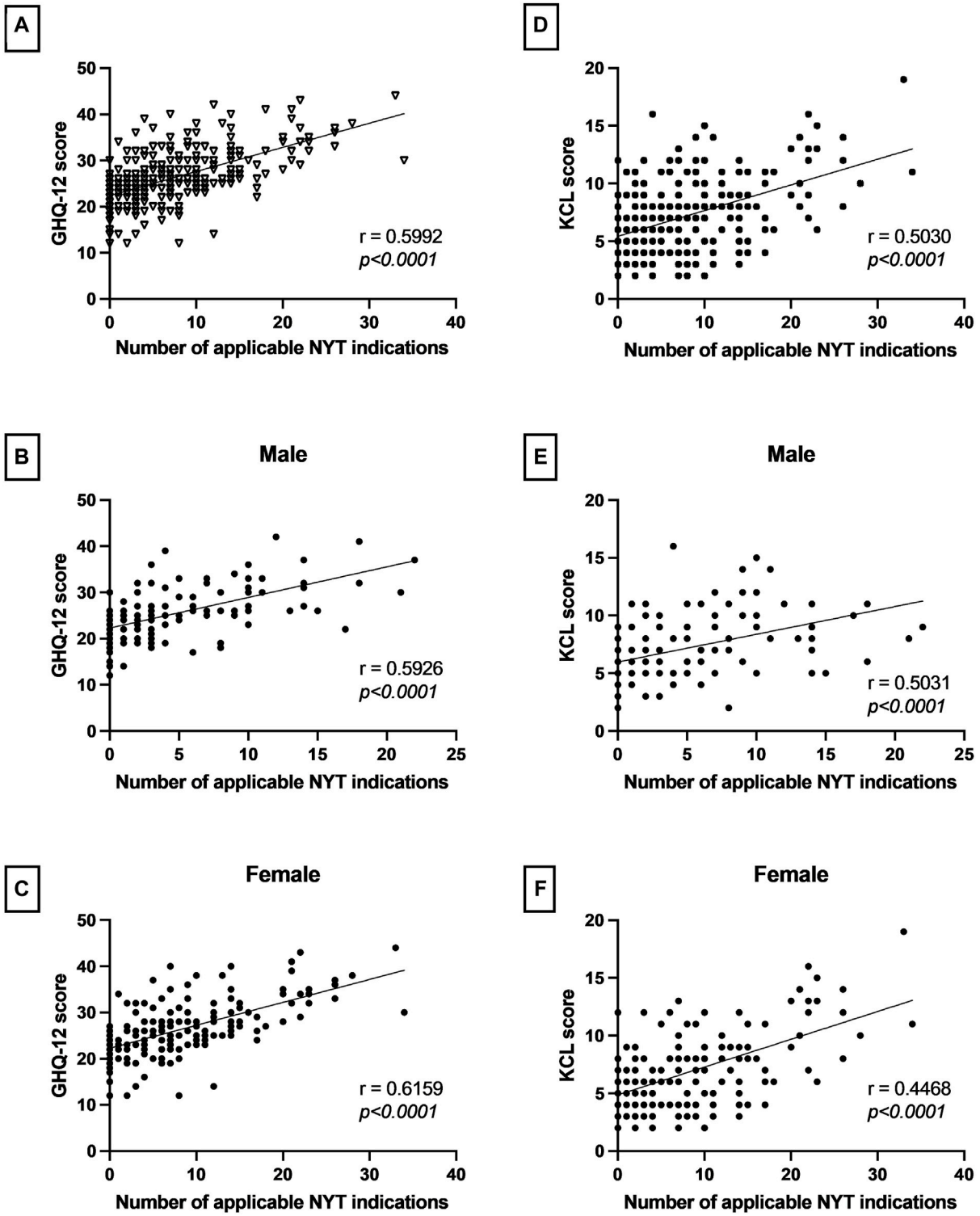

FIGURE 1
The correlations between the number of Ninjin'yoeito (NYT) adaptations and rating scores, both overall and by gender. **(A–C)** The correlation analysis performed in this study showed a significant positive correlation between the number of NYT indications and GHQ-12 scores, both overall and by gender. **(D–F)** Significant positive correlations were also observed between the number of NYT indications and KCL scores, both overall and by gender. These results highlight the significant relationship between the number of applicable NYT indications and both psychological distress and severity of symptom frailty.

applicable NYT indications in the three groups of frail, pre-frail, and robust. The multiple regression analysis was conducted to examine the relationship between the number of applicable NYT indications (dependent variable) and the KCL total score and GHQ12 total score (independent variables), while controlling for age, gender, and BMI as covariates. A multivariate regression analysis was also conducted

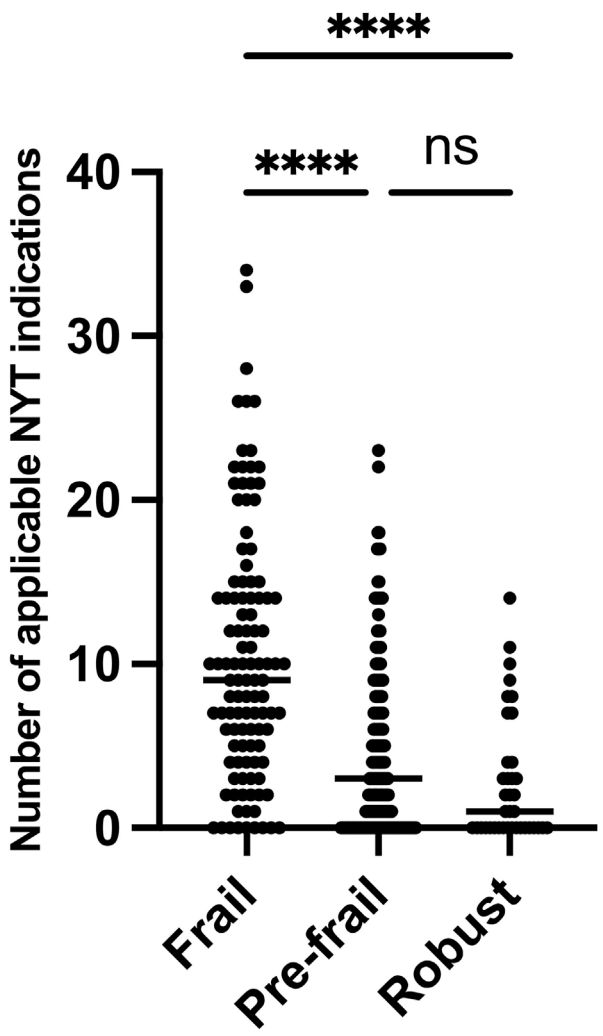

FIGURE 2
Comparative analysis of NYT scores for frail, prefrail, and robust groups. NYT: Ninjin'yoeito.

on the association of GHQ-12 and KCL scores with each of the NYT indications, adjusted for age, sex, and BMI.

Results

The baseline demographic information is shown in Table 2. The sample consisted of 314 participants, with 126 males and 188 females. The median age of the participants was 47.0 years [interquartile range: 41.7–54.0]. The median BMI was 22.0 kg/m^2 [19.7–24.2]. The mean number of NYT applicable indications for males was 3 [0–7.2], while for females it was 6 [1–12]. The median GHQ-12 score for males was 25.0 [21.0–30.0], and for females, it was 25.0 [23.0–29.0]. Additionally, the KCL median score for males was 7 [5–9], and for females, it was 6 [4–8]. None of them reported depression or other psychiatric disorders in their medical history. We tested for normality using the Shapiro-Wilk test and found that only the GHQ-12 total score for males was normally distributed.

As shown in Figure 1, the correlation analysis revealed that there was a strong positive correlation between the number of applicable NYT indications and the GHQ-12 score (r = 0.5953, $p < 0.0001$). Similarly, a moderate positive correlation was observed between the number of applicable NYT indications and the KCL score (r = 0.4289, $p < 0.0001$). When examined by gender, mild to moderate correlations were found. Figure 2 shows that the number of NYT scores was significantly higher in the frailty group than in the pre-frailty and robust groups ($p < 0.0001$).

Multiple regression analysis was conducted to examine the relationship between the number of applicable NYT indications and the independent variables (KCL total score and GHQ12 total score), while controlling for age, gender, and BMI. In the multivariate analysis, both GHQ-12 (β = 0.49, SE = 0.06, t = 7.66, 95% CI: 0.36 to 0.62, $p = 0.000$) and KCL (β = 0.54, SE = 0.12, t = 4.29, 95% CI: 0.29 to 0.79, $p = 0.000$) showed significant positive associations with the variance in the number of applicable NYT indications, indicating that higher scores on these measures were related to a greater number of indications (Table 3A). A multivariate analysis was also conducted on the association of GHQ-12 and KCL scores with each of the NYT measures. The results showed that GHQ-12 scores were significantly associated with physical weakness, general fatigue, and loss of appetite (Table 3B). In addition, KCL scores were significantly associated with anemia in addition to physical weakness, general fatigue, and loss of appetite (Table 3C).

Discussion

To the best of our current understanding, this is the first study to investigate the relationship between the severity of frailty and the degree of adaption to NYT in employees who have underwent a workplace health checkup. The findings of the study indicated a positive correlation between the number of applicable NYT indications and both the KCL total score and the GHQ12 total score.

The implementation of a long-term care insurance (LTCI) system in Japan has been prompted by the fast aging of the population (Tsutsui and Muramatsu, 2007). The LTCI is an insurance system designed to provide support to elderly individuals who are frail or disabled, helping them with their daily tasks. Individuals who are above the age of 65 and require assistance are eligible to receive formal care services, subject to the standards established by the government. The utilization of the Kihon Checklist (KCL) is recommended by the Ministry of Health, Labour and Welfare for the purpose of screening individuals within the target group who are in need of nursing care preventive and Long-Term Care Insurance (LTCI) services. The KCL was developed with the aim of identifying the many health concerns that arise from comprehensive geriatric symptoms. The tool is specifically designed to address the needs of the older population. Additionally, the KCL is utilized to assess the efficacy of interventions implemented (Tsutsui and Muramatsu, 2005; Satake et al., 2016; Sewo Sampaio et al., 2016; Ito et al., 2021). Frailty is frequently delineated by sarcopenia, a debilitating decline in muscle mass, strength, and functionality that also includes various physiological, psychological, and socio-environmental aspects (Rizzoli et al., 2013; Williams et al., 2019). The KCL also

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TABLE 3 (A) Multiple regression analysis of the relationship between the dependent variable Ninjin'yoeito indications and each independent variable, adjusted for age, sex, and BMI. (B) Multiple regression analysis of the relationship between the dependent variable GHQ-12 scores and each independent variable, adjusted for age, sex, and BMI. (C) Multiple regression analysis of the relationship between the dependent variable KCL scores and independent variables, adjusted for age, sex, and BMI.

(A)						
NYT	Univariate	Multivariate				
Variable	*p*	β	SE	t	95%CI	*p*
Age	0.004	−0.00	0.03	−0.02	−0.07 – 0.07	0.982
Sex	0.000	2.78	0.66	4.17	1.47 – 4.10	0.000
BMI	0.066	−0.01	0.01	−0.57	−0.05 – 0.02	0.570
GHQ-12	0.000	0.49	0.06	7.66	0.36 – 0.62	0.000
KCL	0.000	0.54	0.12	4.29	0.29 – 0.79	0.000
(B)						
GHQ-12	Univariate	Multivariate				
Variable	*p*	β	SE	t	95%CI	*p*
Age	0.005	−0.07	0.03	−2.15	−0.13 – 0.00	0.033
Sex	0.238	−0.65	0.61	−1.07	−1.85 – 0.54	0.287
BMI	0.546	−0.00	0.01	−0.28	−0.04 – 0.03	0.781
Physical weakness	0.000	0.66	0.12	4.21	0.35 – 0.97	0.000
General fatigue	0.000	0.84	0.17	4.92	0.50 – 1.18	0.000
Loss of appetite	0.000	0.85	0.24	3.42	0.36 – 1.34	0.001
Night sweats	0.000	0.36	0.19	1.87	−0.01 – 0.75	0.062
Coldness	0.000	0.11	0.11	1.01	−0.10 – 0.34	0.312
Anemia	0.001	0.07	0.26	0.27	−0.44 – 0.59	0.784
(C)						
KCL	Univariate	Multivariate				
Variable	*p*	β	SE	t	95%CI	*p*
Age	0.025	−0.04	0.01	−2.43	−0.07 – 0.00	0.016
Sex	0.319	−1.04	0.32	−3.19	−1.68 – 0.39	0.002
BMI	0.468	0.00	0.00	0.34	−0.01 – 0.02	0.733
Physical weakness	0.000	0.36	0.08	4.31	0.19 – 0.53	0.000
General fatigue	0.000	0.22	0.09	2.50	0.04 – 0.41	0.013
Loss of appetite	0.000	0.51	0.13	3.87	0.25 – 0.77	0.000
Night sweats	0.002	0.01	0.10	1.04	−0.09 – 0.31	0.299
Coldness	0.002	−0.01	0.06	−0.31	−0.13 – 0.10	0.755
Anemia	0.000	0.49	0.14	3.53	0.22 – 0.77	0.000

SE: standard error; 95%CI: 95% confidence interval; BMI: body mass index; NYT: Ninjin'yoeito; GHQ: general health questionnaire; KCL: kihon check list.

conducts assessments in these psychological, and socio-environmental aspects.

The frailty phenotype, as outlined by Fried et al., incorporates data derived from the Cardiovascular Health Study. This comprehensive definition encompasses several key indicators, including unintentional weight loss of 10 pounds within the previous year, self-reported exhaustion, weakness as measured by grip strength, slow walking speed, and low levels of physical

activity (Fried et al., 2001). It is important to note that this definition of frailty is one of the most widely used definitions of frailty. Based on the frailty criteria established by Fried et al., the KCL has strong validity in evaluating frailty (Ogawa et al., 2011; Satake et al., 2016). The study indicated a positive correlation between the number of applicable NYT indications and the KCL total score. The findings of our investigation can be characterized as having unveiled a positive correlation between the number of NYT adaptations and the likelihood of frailty occurrence. Furthermore, the association of KCL scores with NYT application items such as anemia, low physical weakness, general fatigue, and loss of appetite, extends the applicability of the NYT; the KCL assesses a broader range of functional and health-related factors, indicating that the presence of anemia-related symptoms further complicates the complexity of frailty among individuals. The KCL is a multifaceted treatment that is designed to assess the effects of anemia on the health of the individual. This suggests that NYTs with a multifaceted treatment approach may be particularly beneficial in managing the comprehensive symptoms associated with frailty, addressing both physical and psychological aspects, and improving overall quality of life.

While the traditional association between frailty and older adults is widely recognized, an integrative review by Loecker et al. (2021) highlights the presence of frailty in individuals aged 18–65 years, highlighting the multidimensional nature of frailty and the importance of early intervention (Loecker et al., 2021). Complementing this, the UK Biobank study by Hanlon et al. (2018) shows an association between frailty and pre-frailty in a middle-aged population and further advocates preventive measures well before conventional old age (Hanlon et al., 2018). Taken together, these studies support a broader understanding of frailty beyond old age and highlight the potential for early intervention to alter the trajectory of frailty positively. The study's focus on a younger cohort (mean age 47.7 years) is in line with this evolving perspective and is intended to contribute to the basic knowledge about early frailty markers and inform strategies for lifelong frailty prevention. Although the findings in this study relate to a younger cohort, they provide valuable insight into the frailty reserve that may precede more pronounced frailty in later years; direct application to the population aged 65 years and older may be limited by differences in comorbidity profiles and the effects of aging. However, the findings on early indicators in this study are useful for prevention strategies and are consistent with previous literature.

The GHQ-12 is a highly prevalent instrument utilized for evaluating quality of life. According to the previous study, the poor health status of persons exhibiting frailty was found to have a substantial impact on their capacity to participate in various activities (Puts et al., 2007). Consequently, the persons who exhibited frailty had a decline in their overall quality of life when compared to those who did not display frailty (Puts et al., 2007). The finding of our investigation indirectly correspond with the results documented in the previous study. Moreover, it was shown that there exists a positive correlation between the number of applicable NYT indications and the extent of impairment in one's quality of life. This correlation suggests that those who experience more of these symptoms that could potentially be treated with NYT report higher quality of life impairment. This finding highlights the potential for NYT not only to address specific symptoms, but also to improve the overall quality of life of those who exhibit these symptoms. Multivariate analysis revealed a significant relationship between subjective health ratings and the specific symptoms NYT is trying to address: there was a significant association between GHQ-12 scores and symptoms such as low physical weakness, general fatigue, and loss of appetite, suggesting that those experiencing high psychological distress, as measured by the GHQ-12 suggesting that those experiencing high psychological distress as measured by the GHQ-12 were more likely to report these specific physical symptoms. This concordance underscores the interconnectedness of psychological wellbeing and physical health and indicates the potential for the NYT to address both domains simultaneously.

This study has several limitations. First, we used questionnaire-based assessments about physical activity; however, objective assessments such as pedometers and wearable devices should also be considered. Second, this study did not verify the impact of the number of medications taken on frailty. Polypharmacy has been reported to be a risk factor for frailty (Gutierrez-Valencia et al., 2018). Third, this observational study has provided evidence on the correlation between the degree of adaption to NYT and the severity of frailty in employees. However, it is important to note that the study does not establish a causal relationship between these variables. Further investigation is required to clarify the cause-and-effect connection by means of intervention trials conducted on individuals diagnosed with frailty. Finally, the interpretation issues associated with this study were caused by the fact that the population was younger. However, we recognize that this approach has limitations, including a potential gap in direct applicability to persons beyond 65, but we think our findings contribute significantly to our understanding of early frailty indications and preventative efforts.

The deterioration of frailty in elderly individuals is expected to intensify (Lee et al., 2014; Trevisan et al., 2017). Furthermore, there have been reports indicating that it can elevate the likelihood of experiencing negative health consequences, such as long-term care requirements and fatality (Cawthon et al., 2007; Nielsen et al., 2021). However, it should be noted that frailty is a condition that may be reversed and is subject to change throughout time, with the possibility of both improvement and deterioration (Shinkai et al., 2016). There is an expectation that forthcoming breakthroughs would result in further improvements in preventative strategies and appropriate treatments aimed at addressing frailty, a complex condition influenced by several factors.

Conclusion

The findings of our study suggest that NYT has the capacity to offer advantages even in cases of mild and moderate frailty. In a broader sense, NYT has the potential to be utilized not only as a therapeutic intervention for frailty, but also as a form of prevention.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by Ethical Review Committee of Kagoshima University Ethical Review Committee of Kyoto Industrial Health Association. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

HA: Formal Analysis, Writing–original draft, Methodology, Conceptualization. HS: Conceptualization, Writing–original draft, Methodology, Formal Analysis. HK: Writing–review and editing, Resources. MM: Writing–review and editing, Resources. NU: Writing–review and editing, Visualization, Validation. EK: Writing–review and editing, Visualization, Validation. YK: Visualization, Writing–review and editing, Validation. MK: Visualization, Writing–review and editing, Validation. MA: Methodology, Writing–review and editing, Conceptualization. AI: Writing–original draft, Conceptualization, Supervision. YM: Writing–original draft, Conceptualization, Supervision.

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Conflict of interest

YK and MK were employed by Kracie Pharma, Ltd.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Competing risk nomogram predicting cause-specific mortality in older patients with testicular germ cell tumors

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Background: Testicular germ cell tumor (TGCT) is the most common type of malignancy in young men, but rarely in older adults. We aimed to construct a competing risk model to predict the prognosis for older patients with TGCT.

Methods: We collected TGCT patients aged 50 years or older diagnosed between 2004 and 2015 from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database. We estimated the cumulative incidences of cause-specific death (CSD) and other causes of death and established a nomogram predicting cause-specific mortality in older patients with TGCT by Fine-Gray competing risk regression. The concordance index (C-index), calibration curves, area under the receiver operating characteristic curve (AUC), and decision analysis curves (DCA) were used to evaluate the differentiation, accuracy, and clinical significance of the nomogram.

Results: A total of 2,751 older TGCT patients were included in the study. The 3-, 5-, and 10-year cumulative incidences were 4.4, 5.0 and 6.1%, respectively, for cause-specific death, and 3.8, 6.2, 13.1%, respectively, for other causes of death. Predictors of cause-specific mortality in older TGCT included age, marital status, annual household income, histology, tumor size, stage and surgery. In the training and validation sets, the C-indexes were greater than 0.8, indicating that the nomogram had good discrimination. The AUC revealed the same result. The calibration curves showed good agreement between the predicted and observed results of the nomogram. DCA curves indicated that the nomogram had more clinical significance than the conventional American Joint Committee on Cancer (AJCC) staging. Based on the total nomogram score of each case, all patients were categorized into low-risk and high-risk groups, and risk categorization allowed the identification of cases with a high risk of death.

Conclusion: We established a competing risk nomogram with good performance that may help clinicians accurately predict the prognosis of older TGCT patients.

KEYWORDS

competing risk, older patients, testicular germ cell tumors, nomogram, prognosis

Background

Testicular cancer is a relatively rare tumor, accounting for about 1% of newly diagnosed cancers in men worldwide. However, it is the most common malignant tumor in young men aged 14–44 years in Western countries (1). According to the American Cancer Society, there will be around 9,910 new cases of testicular cancer in the United States in 2021, with roughly 460 deaths from the disease (2). Over the last two decades, the global incidence of testicular cancer has grown (3). Testicular germ cell tumor (TGCT) is the most common tumor type among testicular malignancies, accounting for 95% of testicular malignancies, which are divided into seminomatous germ cell tumor (SGCT) and nonseminomatous germ cell tumor (NSGCT). The latter includes four main subtypes: embryonal carcinoma, choriocarcinoma, yolk sac tumor and teratoma, which are all more aggressive than the former (4). There is evidence of a significant age shift towards older age at diagnosis of germ cell tumors, with the average age increasing from 28 to 36 years (5). Several studies have been conducted to determine whether TGCT behave differently in younger and older people. Cancer-specific survival was found to be higher in younger individuals than in older patients (6, 7). This distinction is especially obvious in metastatic disease (8). More importantly, the 5-year survival rate for men diagnosed under the age of 50 is as high as 90%, but less than 70% for men aged 70–79 (6). As a result, precise prognostic prediction for older TGCT patients must be performed.

The AJCC staging system is widely used internationally to evaluate the staging of testicular tumor patients for subsequent therapy options and prognosis assessment (9). However, the AJCC staging system primarily considers anatomical characteristics of the tumor and disregards additional prognostic markers like age and histologic type (10). There is yet no survival prediction model for older TGCT patients. Therefore, it is critical to develop an accurate model to estimate the prognosis of older TGCT patients. Comorbidity and age have a considerable association, which is a competing cause of death in older cancer patients (11, 12). This means that older patients are substantially more likely than younger patients to die from causes other than the target outcomes (13). When evaluating the prognosis of this aged group, competing causes of death should be addressed. In cases where competing risks are present, the naive application of Kaplan–Meier method and standard Cox regression overestimates the proportion of cancer-specific death (CSD) and may result in erroneous risk stratification (14, 15). As a result, competing risk methods are necessary for accurately estimating risk for disease in the older people.

The nomogram is a convenient prognostic tool for estimating survival outcomes that can assist doctors in making personalized decisions for patients through an intuitive graphical model (16). We used the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database to collect information on older TGCT patients for competing risk analysis (17, 18). A competing risk nomogram was also developed to explore the prognostic factors associated with CSD in older TGCT patients. Based on these characteristics, we can predict the probability of CSD in patients and provide a theoretical basis for clinical decision-making.

Abbreviations: TGCT, Testicular germ cell tumors; SEER, Surveillance, Epidemiology, and End Results; C-index, Concordance index; AUC, Area under the receiver operating characteristic curve (AUC); DCA, Decision analysis curves; AJCC, American Joint Committee on Cancer; SGCT, Seminomatous germ cell tumor; NSGCT, Nonseminomatous germ cell tumor; CSD, Cancer-specific death; CIF, Cumulative incidence function; ROC, Receiver operating characteristic; HR, Hazard ratios; CI, Confidence interval; CSS, Cancer-specific survival.

Patients and methods

Data source and data extraction

Male patients over 50 years of age with a diagnosis of TGCT were identified from 17 registries in the SEER database between 2004 and 2015. As we used publicly anonymized data, our study did not require ethical review or patient consent. All methods used in this study were in accordance with the published guidelines of the SEER database. The International Classification of Diseases for Oncology, Third Edition (ICD-O-3) was used to identify cases that meet the histologic type code (9060–9102) and the primary site code (C62.0, C62.1, C62.9). Exclusion criteria included patients younger than 50 years of age, patients with diagnosis confirmed only by autopsy or death certificate or lack of histological confirmation, patients who survived less than one month, and patients for whom information on age, household income, histology, tumor stage, surgery or cause of death were not available. After data selection, the final study cohort consisted of 2,751 cases with a diagnosis of TGCT over the age of 50. For construction and validation of the nomogram, we randomly assigned 2,751 patients to the training and validation cohorts according to a simple random grouping method with a split ratio of 7:3.

We determined the prognostic factors for TGCT in the older people based on demographic and clinical variables such as age at TGCT diagnosis, race, marital status, annual household income, histology, tumor size, AJCC stage, surgery (orchiectomy), radiotherapy, and chemotherapy. In the training and validation cohorts, baseline features were compared using the χ^2 test for categorical covariates, and Mann–Whitney test for continuous covariates. We utilized the X-tile program (Yale University, New Haven, United States) to obtain the best cut-off points. Patients' age was divided into three groups:50–57 years, 58–67 years and ≥ 68 years, tumor size was classified as ≤4.7 cm, 4.8–7.5 cm, ≥7.6 cm and unknown, and annual household income as <$60,000, $60,000–$70,000 and >$70,000. Cancer-specific death was the primary endpoint in the study, defined as death associated with progression of testicular germ cell tumors.

Statistical analysis

We considered cause-specific death and other causes of death as two competing events. The Fine and Gray's test was used to estimate the cumulative incidence function (CIF) and to evaluate significant differences in CIF values between groups. The proportional subdistribution hazard model was used to identify significant variables for CSD and competitive risk nomogram was constructed based on these predictors.

The discrimination of the nomogram is reflected by the concordance index (C-index) and area under the receiver operating characteristic curve (AUC). We also used calibration curves to verify the accuracy of the nomogram. Decision curve analysis (DCA) was

TABLE 1 Baseline clinicopathologic characteristics and treatment experience.

	All cohorts [*n* = 2,751]	Training cohort [*n* = 1,925]	Validation cohort [*n* = 826]	*p* value
Age (years)				0.629
Mean	57	57	57	
Standard deviation	7.3	7.2	7.6	
Race				0.588
White	2,539	1,783	756	
Black	74	49	25	
Other	102	71	31	
Unknown	36	22	14	
Marital status				0.781
Married	1,772	1,248	524	
Not married	819	566	253	
Unknown	160	111	49	
Household income				0.115
<$60,000	679	475	204	
$60,000–$70,000	854	619	235	
>$70,000	1,218	831	387	
Histology				0.679
SGCT	2,241	1,572	669	
NGCT	510	353	157	
Tumor size (cm)				0.561
≤5.4	1,710	1,186	524	
5.5–7.9	519	365	154	
≥8.0	318	233	85	
Unknown	204	141	63	
AJCC stage				0.824
I	2,148	1,497	651	
II	292	208	84	
III	311	220	91	
Surgery				0.217
No	83	53	30	
Yes	2,668	1,872	796	
Radiotherapy				0.187
No/unknown	2,008	1,391	617	
Yes	743	534	209	
Chemotherapy				0.613
No/unknown	1,960	1,366	594	
Yes	791	559	232	

used to assess the net benefit at different risk thresholds to evaluate the clinical utility of the nomogram. Based on the receiver operating characteristic curve (ROC) cutoff value of the total score in the nomogram, patients were categorized into low-risk and high-risk groups. The log-rank test and Kaplan–Meier curves were used to determine differences in survival between groups. The CIF curve was used to visualize the probability of death. All statistical analyses were performed using R software version 4.3.1. A two-sided p value <0.05 was considered statistically significant.

Results

Patients baseline characteristics

As shown in Table 1, there were no statistical differences in demographic and clinical characteristics between the two subgroups (all $p > 0.05$). Table 2 summarizes the demographic and clinical characteristics of the 2,751 eligible older TGCT patients. Across the cohort, the fewest patients were aged 68 years or older (10.0%), with a

TABLE 2 Three-, five-, and ten-year cumulative incidences of death in older patients with TGCT.

Characteristics	*N*	%	Event	%	Cancer-specific death (%)				Death from other causes (%)			
					3-year	5-year	10-year	*p*	3-year	5-year	10-year	*p*
Total	2,751		510		4.4	5.0	6.1		3.8	6.2	13.1	
Age (years)								0.004				<0.001
50–54	1,221	44.4	144	28.2	3.5	3.6	4.4		1.9	3.0	7.2	
55–67	1,255	45.6	238	46.7	5.0	5.9	7.0		4.2	6.6	11.6	
≥68	275	10.0	128	25.1	5.8	7.5	9.4		10.7	19.2	46.0	
Race								0.242				0.174
White	2,539	92.3	470	92.2	4.4	5.1	6.1		3.6	6.1	13.0	
Black	74	2.7	17	3.3	5.4	6.8	10.1		6.8	6.8	16.3	
Other	102	3.7	22	4.3	4.9	4.9	4.9		7.9	11.1	17.1	
Unknown	36	1.3	1	0.2	0	0	0		0	0	0	
Marital status								<0.001				<0.001
Married	1,772	64.4	261	51.2	3.1	3.7	4.4		2.7	4.8	10.7	
Not married	819	29.8	230	45.1	7.7	8.4	10.3		6.3	9.0	18.9	
Unknown	160	5.8	19	3.7	2.6	3.3	3.3		3.2	8.0	10.1	
Household income								<0.001				0.031
<$60,000	679	24.7	152	29.8	6.8	8.4	10.8		4.1	7.0	13.5	
$60,000–$70,000	854	31.0	174	34.1	4.4	4.9	5.7		4.5	7.0	15.0	
>$70,000	1,218	44.3	184	36.1	3.1	3.3	3.8		3.1	5.3	11.6	
Histology								<0.001				0.317
SGCT	2,241	81.5	382	74.9	2.6	3.2	4.1		3.7	6.4	13.5	
NGCT	510	18.5	128	25.1	12.2	13.1	14.6		4.2	5.6	11.1	
Tumor size (cm)								<0.001				<0.001
≤5.4	1,710	62.1	233	45.7	2.3	2.7	3.4		2.2	4.2	10.6	
5.5–7.9	519	18.9	115	22.6	3.3	4.3	6.4		6.2	10.1	16.9	
≥8.0	318	11.6	96	18.8	11.1	12.8	13.6		7.6	10.0	19.1	
Unknown	204	7.4	66	12.9	14.8	14.8	16.0		4.9	7.5	15.5	
AJCC stage								<0.001				0.464
I	2,148	78.1	330	64.7	1.1	1.7	2.7		3.4	6.2	12.9	
II	292	10.6	43	8.4	4.1	4.1	4.7		2.8	3.9	12.0	
III	311	11.3	137	26.9	27.5	28.9	30.9		7.8	8.8	16.3	
Surgery								<0.001				0.812
No	83	3.0	38	7.5	31.3	32.6	34.2		6.0	6.0	13.5	
Yes	2,668	97.0	472	92.5	3.6	4.2	5.2		3.7	6.2	13.1	
Radiotherapy								0.021				0.692
No/unknown	2,008	73.0	387	71.7	5.2	5.7	6.6		4.2	6.5	13.6	
Yes	743	27.0	153	28.3	2.4	3.3	4.5		2.8	5.5	11.9	
Chemotherapy								<0.001				0.187
No/unknown	1,960	71.2	350	64.8	1.5	2.1	3.1		3.5	6.4	13.5	
Yes	791	28.8	190	35.2	11.6	12.3	13.6		4.5	5.8	12.3	

TGCT, testicular germ cell tumor; SGCT, seminomatous germ cell tumor; NSGCT, nonseminomatous germ cell tumor; AJCC, American Joint Committee on Cancer.

majority aged 50–54 years (44.4%) and 55–67 years (45.6%). The dominant population was white (92.3%) and married (64.4%). For most, annual household income was over $70,000 (44.3%). Tumor size was usually less than 5.4 cm (62.1%). Patients were often diagnosed at an early stage (78.1%) and SGCT was the preferred histologic type (81.5%). Surgical treatment was predominant (97.0%), with 743 (27.0%) and 791 (28.8%) patients receiving radiotherapy and chemotherapy, respectively.

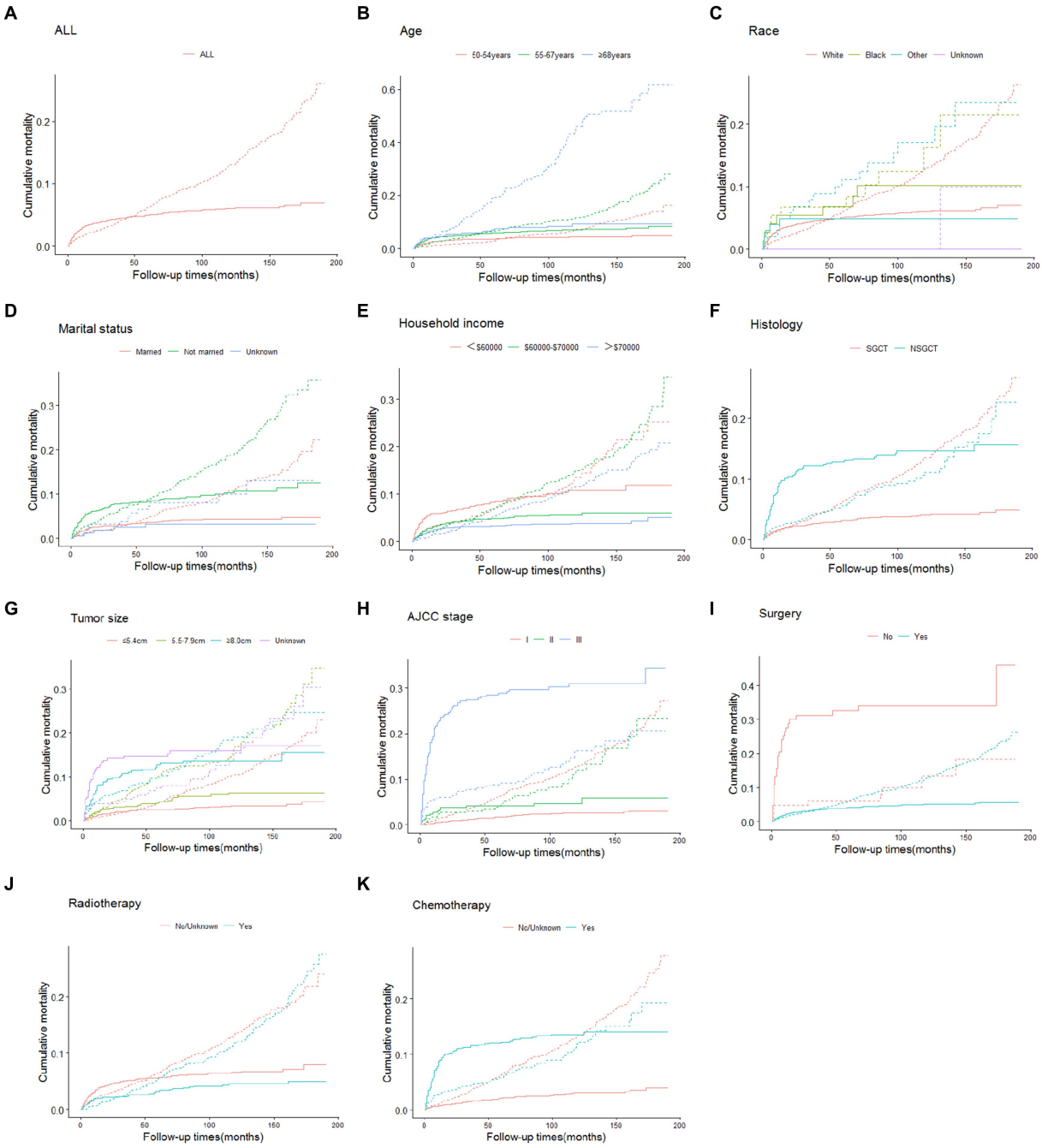

FIGURE 1
Cumulative incidence estimates of death according to patient characteristics (solid line indicates cause-specific death; dotted line indicates other cause of death): all **(A)**; age **(B)**; race **(C)**; marital status **(D)**; household income **(E)**; histology **(F)**; tumor size **(G)**; AJCC stage **(H)**; surgery **(I)**; radiotherapy **(J)**; chemotherapy **(K)**. SGCT seminomatous germ cell tumor, NSGCT nonseminomatous germ cell tumor, AJCC American Joint Committee on Cancer.

The cumulative incidences of cause-specific and other causes of death at 3-, 5-, and 10-year by age at TGCT diagnosis, race, marital status, annual household income, histology, tumor size, stage and treatment are shown in Table 2. The 3-, 5-, and 10-year cumulative incidence for cause-specific of death were 4.4, 5.0 and 6.1%, respectively, among TGCT, and 3.8, 6.2 and 13.1%, respectively, for other causes of death. As shown in Figure 1, the CIF curves indicated that patients who were older, unmarried, at lower annual household income, or with larger tumor size were at risk of dying from TCGT and competing events. Patients with histologic type NSGCT, advanced stage, no surgery or radiotherapy, and who received chemotherapy had an increased cumulative mortality from TCGT, independent of competing causes. There were no statistically significant differences in cancer-specific mortality among races.

Independent predictors of older patients with TGCT

The subdistribution risk ratios (HRs) of the competing risk model for cause-specific mortality in older TGCT are presented in Table 3. Getting older was associated with an increased probability of dying

TABLE 3 Proportional subdistribution hazard models of probabilities of CSD for older patients with TGCT in the training cohort.

Characteristics	HR (95% CI)	*p*
Age (years)	1.03 (1.01–1.06)	0.002
Marital status		
Not married	1.88 (1.26–2.79)	0.002
Unknown	0.71 (0.22–2.31)	0.570
Household income		
$60,000–$70,000	0.64 (0.41–1.00)	0.051
>$70,000	0.45 (0.28–0.71)	<0.001
Histology		
NGCT	2.46 (1.59–3.82)	<0.001
Tumor size (cm)		
5.5–7.9	1.57 (0.92–2.68)	0.098
≥8.0	2.06 (1.25–3.40)	0.005
Unknown	1.93 (1.04–3.58)	0.036
AJCC stage		
II	1.37 (0.71–2.68)	0.35
III	5.85 (3.42–10.00)	<0.001
Surgery	0.47 (0.26–0.87)	0.016
Radiotherapy	1.75 (0.97–3.17)	0.063
Chemotherapy	1.58 (0.91–2.69)	0.100

CSD, cause-specific death; TGCT, testicular germ cell tumor; SGCT, seminomatous germ cell tumor; NSGCT, nonseminomatous germ cell tumor; AJCC, American Joint Committee on Cancer.

from TGCT. Advanced stage (stage III) was a strong predictor of cause-specific mortality. Patients with annual household income >$70,000 and those who had undergone surgery experienced a reduction in cause-specific mortality, with HR of 0.45 (95% confidence interval [CI] 0.28–0.71) and 0.47 (95% CI 0.26–0.87), respectively. Being unmarried was associated with an increased risk of cause-specific mortality, with an HR of 1.88 (95% CI 1.26–2.79). In addition, histology as NSGCT and larger tumor size were linked to poorer outcomes. Radiotherapy or chemotherapy did not predict the probability of cause-specific mortality.

Construction and validation of the nomogram

The nomogram for predicting the probability of CSD in older TGCT patients based on the Fine and Gray's model is shown in Figure 2. For each patient, the values of the different variables are first located in the corresponding rows, and then a vertical line is drawn pointing to the "Points" row to obtain the corresponding scores. By adding these scores together, a total score is obtained and a vertical line is drawn from the total points row to obtain the probability of CSD at 3-, 5-, and 10-year.

The 3-, 5-, and 10-year C-indexes for the nomogram were 0.89, 0.87 and 0.85 in the training cohort and 0.91, 0.89 and 0.88 in the validation cohort, respectively, which suggested excellent model differentiation. In Figure 3, the calibration curves were close to the 45-degree diagonal, indicating that the developed nomogram was well-calibrated (with good consistency between observed and

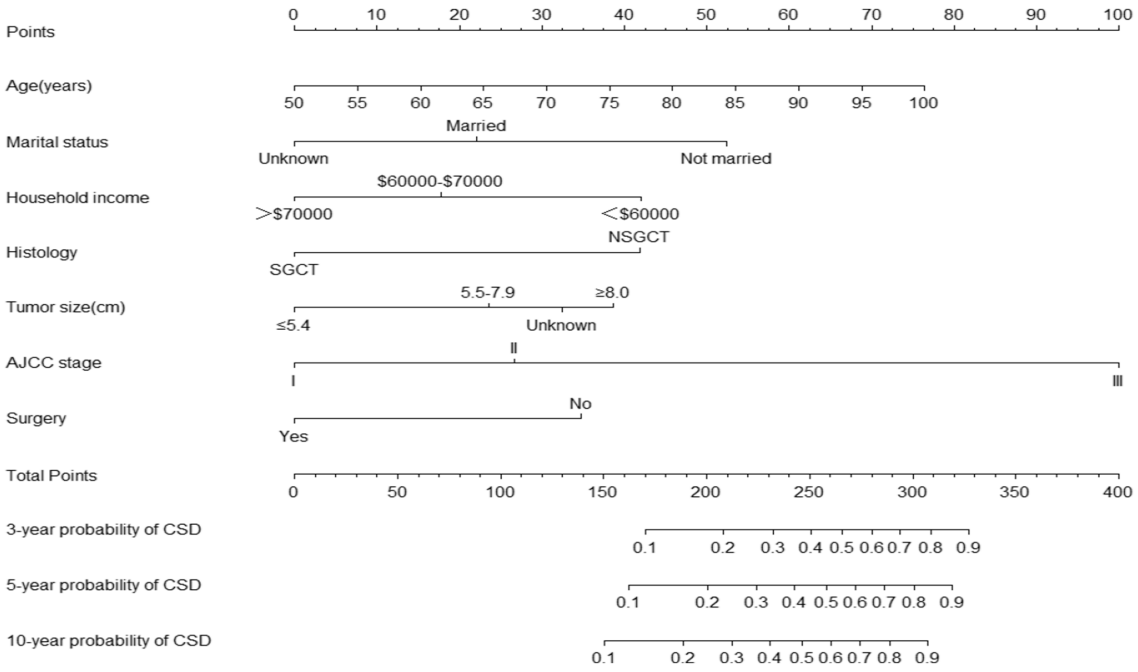

FIGURE 2
Nomogram predicting the probabilities of 3-, 5-, and 10-year cancer-specific death. SGCT, seminomatous germ cell tumor; NSGCT, nonseminomatous germ cell tumor; AJCC, American Joint Committee on Cancer; CSD, cause-specific death.

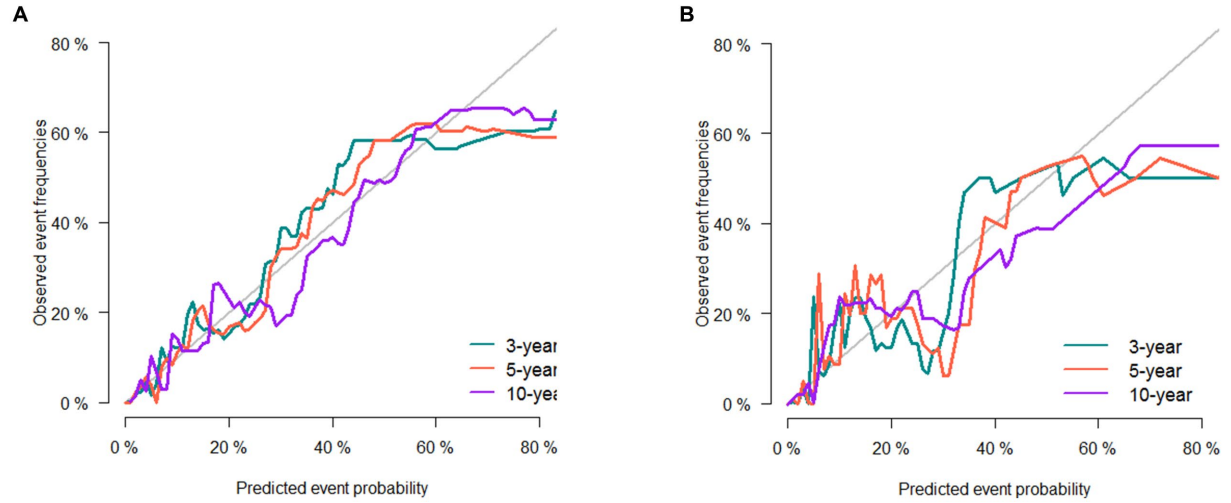

FIGURE 3
Calibration curve of the nomogram in the training set **(A)** and validation set **(B)**. The horizontal axis is the predicted value in the nomogram, and the vertical axis is the observed value.

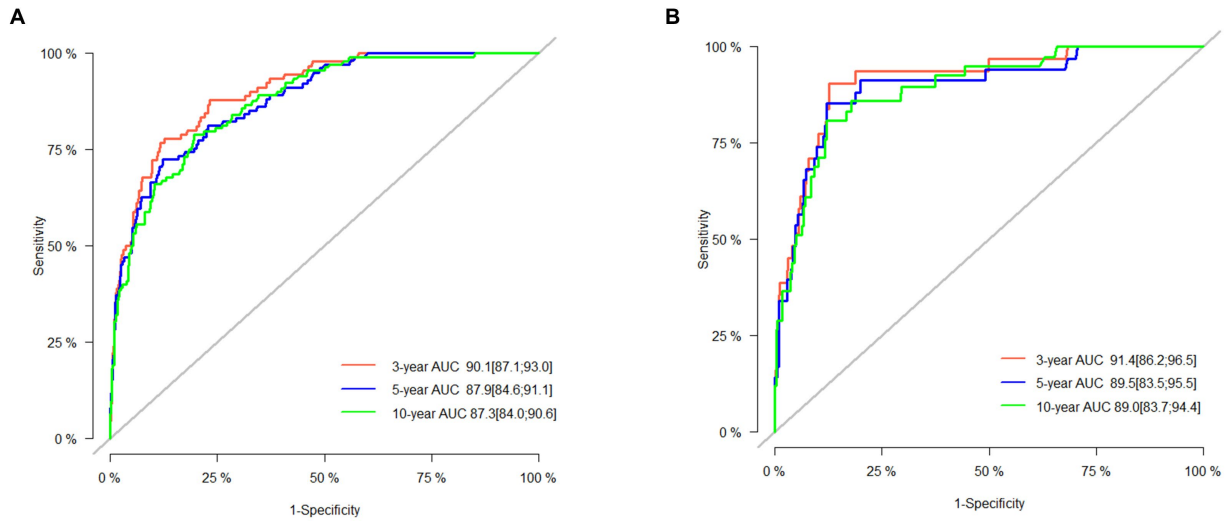

FIGURE 4
AUC for predicting 3-, 5-, and 10-year CSS in the training set **(A)** and validation set **(B)**.

predicted probability of death). As shown in Figure 4, in the training cohort, the AUC values were 90.1, 87.9 and87.3 at 3-, 5-, and 10-year, respectively, while in the validation cohort, the AUC values were 91.4, 89.5 and 89.0 at 3-, 5-, and 10-year, respectively, indicating that the predictive model was well discriminated. DCA curves showed that the clinical value of the nomogram was superior to the AJCC staging system in both the training and validation groups (Figures 5A–F).

We developed a risk stratification system using the ROC cutoff value to categorize patients into two groups: low risk (total score $\leq$ 105.7) and high risk (total score > 105.7). As depicted in Figure 6, the cancer-specific survival (CSS) was lower in the high-risk group than in the low-risk group, and the probability of CSD was higher in the high-risk group than in the low-risk group (both $p < 0.0001$). The 3-, 5-, and 10-year CSS in the high-risk group were 98.9, 98.4 and 97.8%, respectively, compared with 83.9, 82.8 and 79.5% in the low-risk group. The 3-, 5-, and 10-year CSD for the high-risk group were 15.5, 16.5 and 19.3%, respectively, and 1.1, 1.6 and 2.2% for the low-risk group.

Discussion

There is no consensus on the age definition of older TCGT patients. However, the relative survival of TGCT patients aged $\geq$50 years was significantly lower than that of patients aged <50 years and was characterized by distinct clinical features in terms of histologic type and stage (19, 20). Consequently, we defined the age criterion for older patients in this study as 50 years. We calculated the CIF for cause-specific and competitive risk of death in older TGCT patients. In the case of competing risks, the CIF provides an unbiased

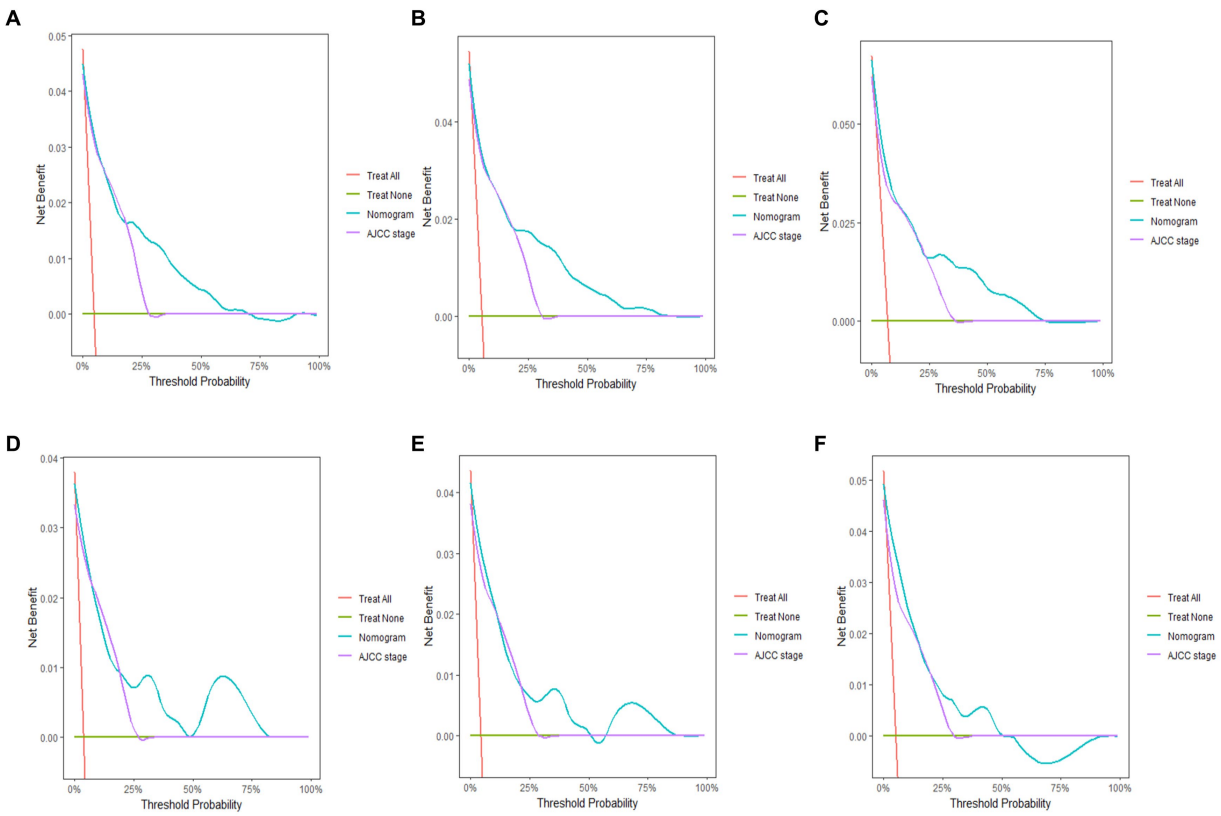

FIGURE 5
Decision curve analysis of the nomogram. Y-axis represents a net benefit and x-axis represents threshold probability. The green line means no patient died and the red line means all patients died. **(A)** 3-year survival benefit for the training cohort. **(B)** 5-year survival benefit for the training cohort. **(C)** 10-year survival benefit for the training cohort. **(D)** 3-year survival benefit for the validation cohort. **(E)** 5-year survival benefit for the validation cohort. **(F)** 10-year survival benefit for the validation cohort.

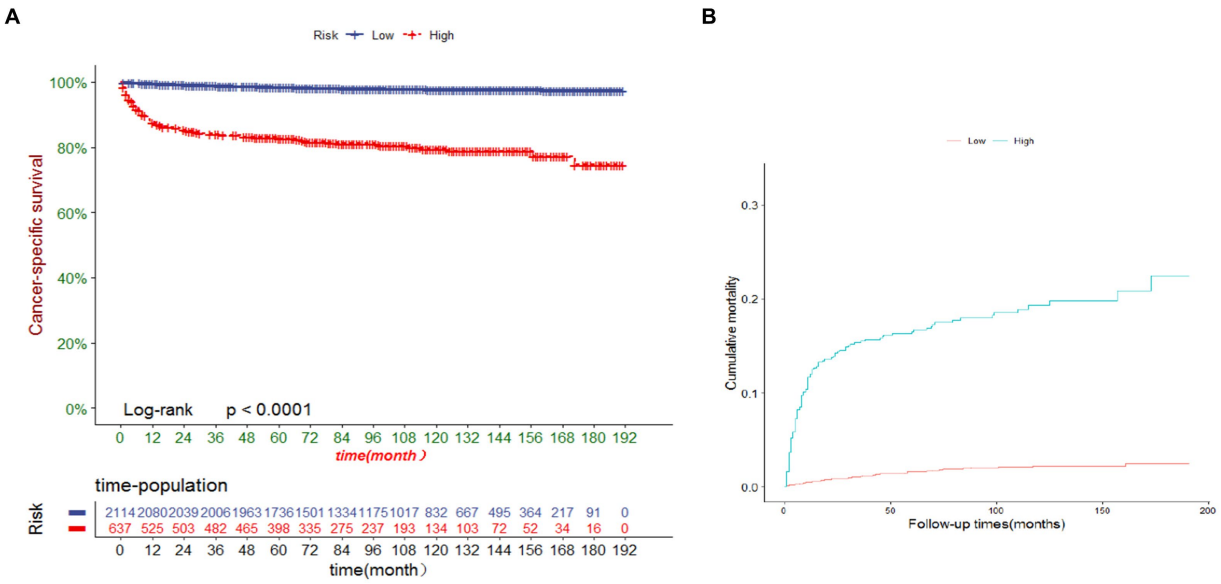

FIGURE 6
(A) Cancer-specific survival and **(B)** cumulative incidence of cause-specific death for patients in the low-risk and high-risk groups.

estimate of the probability of a certain event (14). To the best of our knowledge, this is the first study to attempt to build a nomogram for predicting CSD in older TGCT using a proportional subdistribution risk approach based on population data. The nomogram can be immensely helpful for clinicians in caring for older patients with TGCT to discuss treatment modalities and prognosticate. After obtaining basic information about the patient such as age, marital status, annual household income, and diagnostic information such as histologic type, tumor size, and AJCC stage, the treatment can be discussed based on the nomogram. After the patient has undergone treatment, the physician can again predict the patient's prognosis based on the nomogram.

In our competing risk model, age, marital status, annual household income, histology, AJCC stage, tumor size, and surgery had a significant effect on CSD in older TGCT patients. Age is associated with the prognosis of most malignant tumors. Many studies have shown that increasing age is linked with recurrence, metastasis, and mortality in TGCT. According to a recent report by the International Germ Cell Cancer Cooperative Group (IGCCG-Update Consortium), the risk of progression increases by 25% for each decade of life expectancy in metastatic NSGCT (21). In comparison to younger patients, Fosså SD et al. discovered a significant twofold increase in TGCT-specific mortality in men over 40 years of age (8). Similarly, data from the Danish Population-Based Cancer Registry indicated that age could be a new prognostic factor for TGCT recurrence and mortality. Aging for 10 years increases the risk of death due to TGCT by 1.3-fold (22). In this study, socioeconomic-related factors, such as annual household income, was also a risk indicator for patient mortality. Consistently, existing publications have shown that TGCT patients with lower socioeconomic status are more likely to have advanced disease as well as higher overall and cancer-specific mortality compared to cases with higher socioeconomic status (8, 10, 23). In addition to annual household income, marital status was employed as one of the predictors for the CSD in this study. Previous studies have shown that unmarried men had two- to three-fold excess mortality compared to married men (8, 24). Potential mechanisms may include earlier detection, improved compliance, and more social support for married TGCT patients (24).

Our study demonstrated that staging is a significant prognostic variable in older TGCT patients, which is consistent with a previous retrospective report from a large cohort. Patients with advanced stage (stage III) tend to have a higher probability of CSD. The previous study showed that TCGT patients with AJCC stage III exhibited the highest 5-year CSD (SGCT: stage I:0.4; stage II:3.4; stage III:11.4%; $p < 0.01$; NSGCTT: stage I:1.6; stage II:2.5; stage III 22.2%; $p < 0.001$) (25). Meanwhile, we discovered that patients with a histologic type of NSGCT had a worse prognosis compared to SGCT. Patients with TGCT in the presence of distant metastasis predominantly present with NSGCT (21, 26). The poor outcome of TGCT is mainly driven by distant metastasis. The presence of lung metastasis implies a 62% increased risk of progression compared to NSGCT patients without lung metastasis. Patients who had non-pulmonary visceral metastases to the bone, liver, or brain had a 5-year progression-free survival of less than 78% (21). Furthermore, those patients carrying brain metastasis demonstrated the worst survival rates, with more than half of them experiencing disease progression and death within one year of confirmed intracranial involvement (27).

In our study, tumor size has also been identified as an independent predictor of TGCT in older adults. Larger tumor size tends to suggest a poor prognosis. Several investigators have found that tumor size is related with recurrence in clinical stage I NSGCT cohorts, with significant thresholds of 4 cm and 5 cm (28, 29). A study including 219 patients with NSGCT demonstrated that tumor size was a strong predictor of metastatic disease at the time of diagnosis, with a significant threshold of 6 cm (30). However, several other studies have not consistently shown a substantial association (31, 32). Different from NSGCT, tumor size in SGCT is a well-known prognostic factor for advanced clinical stage and metastatic disease.

Radical orchiectomy is the primary treatment for most patients with TGCT (33). After evaluating the relationship between age and outcomes in colon, lung, hepatobiliary, and head and neck cancers, several researchers concluded that surgery remains the best treatment for solid tumors and the actual age itself should not be a determining factor in therapeutic decisions (34). Our study confirmed that surgical treatment was a protective factor in older TGCT patients, with a remarkably better prognosis than the non-surgical treatment group. Currently, there is still no consensus on adjuvant treatment options TGCT in the older people after orchiectomy. Our data showed that radiotherapy improved patients' survival, whereas chemotherapy had the reverse result. However, after adjusting for confounders, they could not be used as prognostic predictors. Historically, adjuvant radiotherapy or chemotherapy aimed to reduce the probability of recurrence in patients with TGCT for the sake of improving survival (34). Nevertheless, there is evidence that radiotherapy or chemotherapy has adverse effects on TGCT. A previous study revealed that radiotherapy or chemotherapy increased the risk of developing a second malignancy by 2.6 times after radiotherapy and 2.1 times after chemotherapy (35). Furthermore, a recent study reported that patients treated with cisplatin, bleomycin, and etoposide alone had a 5.7-fold higher risk of cardiovascular disease compared with patients who received surgery only (36). Another report based on a cohort of 453 male patients with SGCT who underwent orchiectomy and radiotherapy showed a standardized mortality rate (SMR) of 1.59 (99% CI 1.21–2.04), with a significant increase after 15 years of radiotherapy (37). Especially in the older people, toxicity may be generated at lower doses of radiation due to altered organ function and the presence of concomitant diseases (38). On the contrary, some other studies have shown the opposite results (39, 40). Since testicular cancer is rare in the older people, there are little data on the clinical characteristics and prognosis of patients with TGCT after the age of 50 years. Therefore, prospective studies should be designed specifically for the older people in order to develop optimal treatment regimens for them.

TGCT is a rare malignancy in the older people, making it challenging to assess its prognosis. The SEER database is able to provide a sufficiently large and representative sample. We established this nomogram using the SEER database and verified its validity. Taken together, our nomogram may be a useful method for assessing the prognosis of older TGCT patients. In addition, the risk stratification of our nomogram helps to identify high-risk groups, thereby providing them with appropriate clinical guidance.

However, there are some deficiencies in this study. First, the SEER database lacks other crucial variables such as lifestyle, genetic background, and environmental factors that may influence the prognosis of older TGCT patients. Second, as a retrospective study,

selection bias may be inevitable. For example, the subjects of this study were mainly focused on high-income groups and Caucasians, which may have reduced the breadth of our results. Instead, we incorporated important parameters such as age, stage and treatment to ensure that the results were not considerably biased. Third, we were unable to obtain detailed information about cancer recurrence and treatment, which hindered further analysis. Finally, although our model exhibited excellent performance in predicting the probability of CSD in older TGCT patients, prospective validation in a multicenter study is needed to confirm the accuracy of the model.

Conclusion

In summary, this study establishes a valuable nomogram for the prediction of CSD in older TGCT patients, which may provide a meaningful reference for the treatment of this special population.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving humans were approved by the data of this study is obtained from the SEER database. The patients' data is public and anonymous, so this study does not require ethical approval and informed consent. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

XW: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Validation, Visualization, Writing – original draft. MZ: Writing – original draft. JL: Supervision, Writing – review & editing. LC: Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Optimizing clinical outcomes in polypharmacy through poly-de-prescribing: a longitudinal study

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Objectives: To evaluate polypharmacy in older people to determine whether the number of medications de-prescribed correlates with the extent of improvement in quality of life (QoL) and clinical outcomes.

Design: A prospective longitudinal cohort study of polypharmacy in people living in a community in Israel.

Setting: Participants aged 65 years or older who took at least six prescription drugs followed up for at least 3 years (range 3–10 years) after poly-de-prescription (PDP) recommendations.

Interventions: PDP recommended at first home visit using the Garfinkel algorithm. Annual follow-up and end-of-study questionnaires used to assess clinical outcomes, QoL, and satisfaction from de-prescribing. All medications taken, complications, hospitalizations, and mortality recorded. In total, 307 participants met the inclusion criteria; 25 incomplete end-of-study questionnaires meant 282 participants for subjective analysis. Participants divided into two subgroups: (i) those who discontinued more than 50% of the drugs (PDP group) or (ii) those who discontinued less than 50% of the drugs (non-responders, NR).

Main outcome measures: Objective: 3-year survival rate and hospitalizations. Subjective: general satisfaction from de-prescribing; change in functional, mental, and cognitive status; improved sleep quality, appetite, and continence; and decreased pain.

Results: Mean age: 83years (range 65–99years). Mean number of drugs at baseline visit: 9.8 (range 6–20); 6.7±2.0 de-prescribed in the PDP group (n=146) and 2.2±2.1 in the NR group (n=161) (p<0.001).

No statistical difference between the groups in the 3-year survival rate and hospitalizations, but a significant improvement in functional and cognitive status and, in general, satisfaction from the intervention in the PDP group compared to the NR group. Improvement usually evident within the first 3 months and persists for several years.

Conclusion: Poly-de-prescribing in the older population has beneficial effects on several clinical outcomes with no detrimental effect on the rate of hospitalization and survival. The extent of improvement correlates with the extent of de-prescribing. Applying the Garfinkel algorithm globally may improve QoL in millions of patients, a clinical and economic win–win situation.

KEYWORDS

poly-de-prescribing, polypharmacy, inappropriate medication use, geriatric palliative approach, multi-morbidity, dementia, frailty

Introduction

Advanced successful healthcare systems, despite their many advantages, also brought about a "tidal wave" of inappropriate medication use and polypharmacy (IMUP) as a result of a phenomenal rise in the number of specialists and medications, as well as over-diagnosis. IUMP may be problematic for vulnerable populations, in particular for the VOCODFLEX (a term previously coined by us) group that represents Very Old people, with COmorbidity, Dementia, Frailty/disability, and with limited Life EXpectancy (1–3). Quite clearly, IMUP has become a worldwide problem. Unlike pandemics, for which immunization and/or treatment is rapidly found within several years, no consensus exists regarding the best way to address the problem of IMUP and we seem to be losing the war against this insidious, century-old iatrogenic condition (1–4).

The reason for this medical failure is probably multifactorial and involves fundamental mistakes in our traditional research and clinical perceptions, conflicts of interest, and psychological inhibitions in both health professionals and the general public. A series of efforts and monetary resources have been expended for several decades to find ways to suppress IMUP (5–10). Unfortunately, these efforts led to only minor improvements in clinical outcomes, with no large absolute reduction in drugs, if any (2, 4, 11). Lack of evidence supporting the benefits of de-prescribing may explain why many physicians, although being aware of the harmful consequences of IMUP, are reluctant to routinely de-prescribe (12).

Our hypothesis is that the clinical harm resulting from IMUP outweighs the sum total of all the beneficial effects of the specific drugs and combinations of drugs de-prescribed.

The main determinant of IMUP is the absolute number of drugs (13–17). The present study was designed to evaluate the effect of long-term de-prescribing on the quality of life (QoL), clinical outcomes, survival, and rate of hospitalizations in older people. To our knowledge, this is also the first longitudinal study attempting to establish that, regardless of the types of drugs discontinued, the extent of de-prescribing itself correlates with the extent of benefit in clinical outcomes and QoL.

Methods

This longitudinal cohort study included patients living in a community and over 65 years of age, who were taking at least six prescription drugs that did not include vitamins, minerals, food additives, topical preparations, and over-the-counter medications. Patients were referred to the consultant geriatrician (DG) for a comprehensive geriatric assessment (CGA) or specifically for de-prescribing. Exclusion criteria were life expectancy shorter than 6 months and the inability of the patient or their family to adhere to an orderly, long-term follow-up. Patients were enrolled in the study beginning in 2009 and all were followed up for at least 3 years until 2019 (3–10 years follow-up).

Baseline visit

During the first visit, the geriatrician resorted to a detailed data collection and performed CGA, including an evaluation of all the prescription and non-prescription medications. All patients were subjected to a full physical examination and an up-to-date laboratory evaluation. Functional status was determined using a 5-point scale, modified from the traditional Fried's phenotype model (18):1 = independent, 2 = frail 3 = mild disability [needs help in 1–2 activities of daily living (ADLs)]; 4 = disability (needs help with at least 3 ADLs); 5 = severe disability/bedridden. Cognitive status was assessed using the Mini Mental State Examination (MMSE) test. Depression was assessed using the Geriatric Depression Scale (GDS) short form except for patients with severe dementia.

Poly-de-prescribing process

De-prescribing of medications was done using the Garfinkel method; it postulates that in older people, the appropriateness of continuing each drug on a patient's prescription list should be thoughtfully considered. This is done using the Garfinkel algorithm de-prescribing tool (Figure 1) (19, 20). The method combines evidence-based medicine research data (when exists) with particular characteristics of the patient/family (e.g., values, beliefs, and functional and cognitive status), placing their preferences as the highest priority. Improving QoL as perceived by the patient/family takes precedence over achieving chronic disease care targets (e.g., blood pressure [BP] level, serum glucose, and lipid concentrations). Collaboration with the family/patient is therefore central to the Garfinkel method, which requires devoting time to addressing their concerns and providing explanations. Taking into consideration the known literature for each drug and risks of polypharmacy, we advise the patient/family on poly-de-prescribing (PDP) recommendations and receive their consent to stop as many non-life-saving drugs as possible. These may include preventative medications (e.g., antihypertensive medications [AHT], cholesterol-lowering drugs, aspirin, anticoagulants), as well as drugs for relieving symptoms such as sleeping pills, drugs for dyspepsia, or vertigo. Drugs from different groups are discontinued simultaneously while drugs prescribed for the same indication (e.g., AHT) are stopped one drug at a time with a detailed plan. Detailed verbal and written recommendations are provided to the patient/family, along with supporting references to the family doctor/general practitioner (GP). In this study, all participants were given individual recommendations for PDP from the same geriatrician.

Follow-up

All patients/families were contacted by phone at least once a year and their comments recorded regarding their health status and any change in symptoms and signs. Furthermore, every drug that was discontinued was also followed up for undesirable adverse effects (AE). For example, when discontinuing proton pump inhibitors (PPIs) or H2 blockers, participants were followed for gastrointestinal bleeding or dyspepsia; when medications for Parkinson's disease were gradually de-prescribed, patients were evaluated for deterioration in extrapyramidal symptoms/signs and/or functional decline.

In all the participants, an end-of study questionnaire (Appendix 1) was administered between March 2017 and October 2019. At that time, all the patients had at least 3 years of follow-up

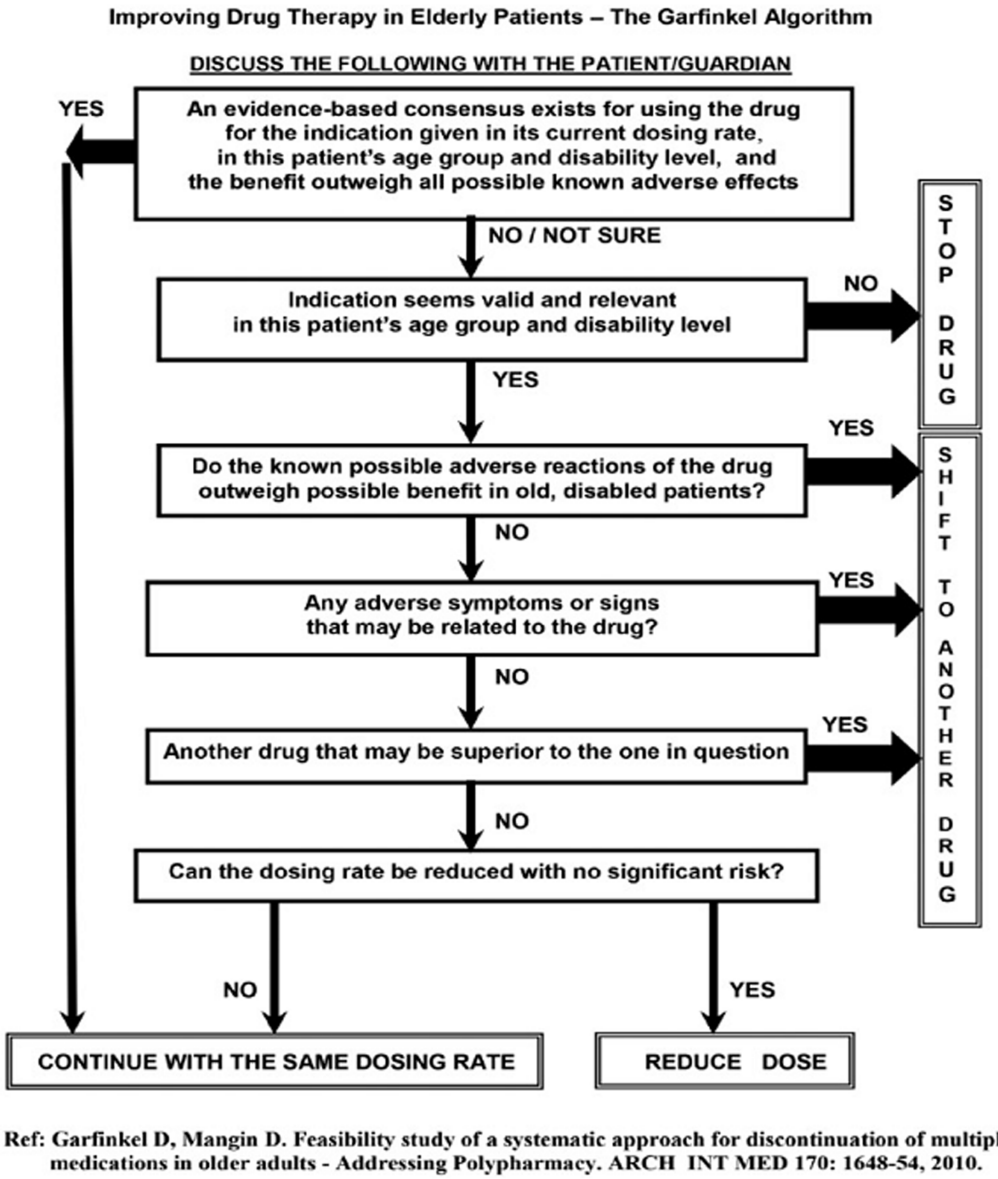

FIGURE 1
Improving drug therapy in older people: the Garfinkel algorithm.

(Maximum 10 years). Participants were required to assess the change between the first CGA visit and their last follow-up interview on several clinical outcomes using a 5-point Likert scale (1 = much improved, 2 = improved, 3 = no change, 4 = worsened, 5 = much worse). The parameters for evaluation were overall satisfaction from the PDP approach, functional, mental, and cognitive status, nighttime sleep quality, daytime sleepiness, appetite, pain, and incontinence. These were all *subjective* scores, based on the patient's perception, or family/primary caregiver's impression when patients had severe dementia or disability. Patients/families were also asked to report *objective* parameters: all types of medications taken, new diagnoses, complications, and hospitalizations since the first CGA visit. These were confirmed by medical documents. Mortality was assessed based on formal data obtained from the Ministry of Internal Affairs through October 2019. The study was started in 2009 and ended in October 2019.

The study protocol was approved in 2009 by the ethics committees of the Shoham Geriatric Medical Center, Pardes-Hana, and later the Wolfson Medical Center, Holon, Israel (ID 0068-15-WOMC SERIAL No. 57077, 9/7/2015). Being an improved quality CGA stressing on the evaluation of medications, a written informed consent was not required by the ethics committees. Only the authors (researchers) were aware of the specific demographic and medical details, and confidentiality of all patients was maintained throughout the study.

Statistical analysis

Data were analyzed with IBM SPSS statistics software version 25.0 (SPSS Inc., Chicago, IL, USA). All tests were two-tailed and the significance levels were set at 0.05. Baseline characteristics and chronic diseases were presented as means and standard deviations for

continuous variables and as frequencies and percentages for categorical variables. Spearman correlations were calculated for continuous variables.

The study population was divided into two groups based on the rate of de-prescribing. The poly-de-prescribers group (PDP) included those who discontinued more than 50% of the drugs taken at the baseline visit, and the control group was termed the non-responders (NR) group, which included older people who discontinued 50% or less of the medications they were taking at the baseline visit.

The chi-square tests were performed to compare the changes in the main clinical outcomes and QoL parameters between groups (PDP group Vs. NR group). Independent t-tests were performed to compare the two groups for continuous variables. For our observational study, the assignment of subjects into groups was not random but rather done based on the number of medications de-prescribed. In an attempt to reduce the group assignment bias and mimic randomization in order to create groups that are comparable on all observed covariates, we adjusted for the propensity score (PPS). We calculated PPS using a logistic regression model with the observed confounders at baseline (age, gender, family status, number of children, health and functional status at baseline, and number of diseases and prescribed drugs at baseline). Odds ratio (OR) and 95% confidence intervals for PDP were compared to NR for the main outcomes (patient/family satisfaction and clinical outcomes, as dichotomous variables improved/not improved) and were adjusted for PPS. The length of follow-up was calculated as the time from the first baseline visit until death or until the last follow-up visit, in those who were still alive. We used the Cox proportional hazards regression models to evaluate the hazard ratios (HR) and 95% confidence intervals for death among groups, adjusted to PPS. The only variable entered into the model was PPS (which already includes different variables as explained in the Methods section).

Results

A total of 307 patients met the inclusion criteria for the study. The mean age of the patients was 83 years (SD = 5.95; range 65–99 years), and 35% were men. The extent of multi-morbidity on baseline visit was reflected by a mean number of diseases/geriatric syndromes of 10.4 (SD = 2.9, range 2–18); the mean number of drugs at baseline was 9.8 (SD = 2.6, range 6–20), thus reflecting the extent of polypharmacy. The Mini Mental State Examination (MMSE) score was 23.3 ± 8.5 (range 5–30); the Geriatric Depression Scale (GDS) score was 6.94 ± 4.35 (range 1–14). There was no significant difference between men and women for these characteristics. Data on weight were available in 215 participants (range 39–110 kg); it was significantly higher in men as compared to women (77 ± 12 versus 64 ± 12 kg, respectively).

The study population was consuming a variety of drugs from several groups, often more than one medication for the same indication (particularly antihypertensive medications [AHT]). Table 1 describes the most common medications used by all participants at baseline visit, the number of those de-prescribed, and the number of medications that have actually been discontinued at the end of follow-up. For instance, out of 243 participants who were on statins, 154 (63%) eventually stopped using them. Stopping slow-release nitrates was recommended in 19 patients out of 20 who were taking them and achieved in 13 (68%); none of them experienced angina pectoris or electroencephalogram (ECG) changes, and no one needed the sublingual nitroglycerin that had been provided as a means of precaution for PRN (*pro re nata*, as needed) use. None of the older patients for whom PPIs or H2 blockers were de-prescribed experienced gastrointestinal bleeding. Out of 73 patients who were diagnosed as having Parkinson's disease, none of the 23 (32%) patients in whom anti-Parkinsonian medications had been de-prescribed experienced deterioration in function or in extrapyramidal symptoms or signs. Subsequent reductions in serum hemoglobin concentration were not found in any of those in whom iron was stopped.

In the subgroup analysis of objective parameters, 146 patients reduced the number of drugs by more than 50% from baseline (designated the PDP group) and 161 patients reduced the number of drugs by 50% or less (NR, control group). The PDP group was significantly older than the NR group (84.45 ± 5.76 vs. 81.85 ± 5.86; $p < 0.001$). The PDP group had lower rate of hypertension and higher rate of incontinence and dementia (Table 2). With regard to all other health problems, the groups were comparable.

Table 3 summarizes the objective long-term effects of poly-de-prescribing. Both groups were followed up for an average of 57 months.

In spite of a significantly higher number of de-prescribed medications in the PDP group, there was no change in the objective end points and no increase in the rate of hospitalizations or mortality. The PPS-adjusted Cox proportional survival curves were the same for both groups (Figure 2, OR 0.960; 95% C.I. [0.695–1.324], $p = 0.802$).

Out of the 307 participants enrolled in the study at the first visit, completely reliable full end-of-study questionnaires could not be obtained from 25 participants. Therefore, we performed the *objective* parameter analysis for all the 307 participants of the cohort study (Tables 1–3), but comparison of the *subjective* parameters was based on data from 282 participants only (Table 4).

We observed more significant improvements in outcomes among the PDP group as compared to the NR group in terms of patient/family satisfaction, self-perceived health, functional and cognitive status as well as nighttime sleep quality and daytime wakefulness. No subjective deterioration was observed for any of the outcomes in the PDP group as compared to the NR group (Table 4). Although the rate of mental status improvement was higher among the PDP group patients in univariate analysis (two times more improvement), the difference between the groups was not statistically significant in the multivariate analysis (possibly due to relationships to other variables in the model). As for the initiation, length, and extent of clinical improvement, high satisfaction and significant improvement in clinical outcomes were already apparent in 71% of the patients in the PDP group within the first 3 months of follow-up as compared to only 34.5% of the patients in the NR group; the improvement persisted more than one year in 70% of the PDP participants as compared to only 35% in the NR group ($p < 0.001$ in both parameters). Among those patients surviving longer than 2 years, 52% in the NR group reported a worsening in their clinical status compared to only 28% of the PDP group ($p < 0.001$).

Discussion

Modern medicine has prolonged life expectancy and with it a growing VOCODFLEX population (as defined by us previously)

TABLE 1 Rate of de-prescribing for specific medications/drug groups.†

	Total $n = 307$ (%)	De-prescribing suggested (%)	De-prescribing achieved (%)
Calcium channel blockers	136 (44)	127 (93)	63 (46)
Beta-blockers	182 (59)	48 (26)	50 (27)
Angiotensin-converting enzyme inhibitors	112 (36)	81 (72)	51 (45)
Angiotensin II receptor blockers	106 (34)	61 (57)	30 (28)
Hydrochlorothiazide	79 (26)	70 (88)	54 (68)
Furosemide	73 (24)	50 (68)	28 (38)
Spironolactone	22 (7)	15 (68)	10 (45)
Alfa blockers	79 (26)	79 (100)	44 (55)
Clonidine	7 (2)	5 (71)	3 (42)
Slow-release nitrates	20 (6)	19 (95)	13 (65)
Amiodarone	28 (9)	11 (39)	11 (39)
Digoxin	6 (2)	2 (33)	2 (33)
Acetyl Salicylic acid (Aspirin)	186 (61)	133 (71)	104 (55.9)
Warfarin (Coumadin)	46 (15)	13 (28)	16 (34)
Enoxaparin	4 (1)	4 (100)	4 (100)
Clopidogrel	52 (17)	12 (23)	18 (34)
DOAC*	14 (5)	1 (7)	1 (7)
Sulfonylurea	22 (7)	22 (100)	13 (59)
Metformin	75 (24)	43 (57)	23 (30)
Repaglinide	26 (8)	21 (80)	9 (34)
DPP4 inhibitor **	19 (6)	11 (57)	4 (21)
Insulin	26 (8)	3 (11)	2 (7)
Statins	243 (79)	235 (96)	154 (63)
Fibrates/Ezetimibe	14 (5)	14 (100)	4 (28)
Thyroid hormones	72 (23)	1 (1.4)	7 (9.7)
Allopurinol	17 (5)	11 (64)	9 (53)
Proton pump inhibitors (PPI)	173 (56)	151 (87)	73 (42)
H2 Blockers	37 (12)	35 (94)	24 (64)
Benzodiazepines	219 (71)	205 (93)	126 (57)
Z-Drugs ***	43 (14)	24 (55)	17 (39)
SSRIs/SNRIs ^^	124 (40)	118 (95)	65 (52)
Trazodone	6 (2)	3 (50)	4 (66)
Amitriptyline	9 (3)	7 (77)	0 (0)
Mirtazapine	38 (12)	18 (47)	15 (39)
Duloxetine	24 (8)	10 (41)	8 (33)
Diphenyl-hydantoin (Phenytoin)	1	1 (100)	1 (100)
Carbamazepine	3 (1)	2 (66)	2 (66)
Valproate	5 (2)	1 (20)	2 (40)
"Other" Anti-Epileptics ^^^	9 (3)	6 (66)	4 (44)
Haloperidol	3 (1)	1 (33)	1 (33)
Anti-Psychotics (typical and atypical)	38 (12)	24 (63)	17 (44)
Anti-Vertigo Drugs ^	22 (7)	21 (95)	16 (72)
Amantadine	11 (50)	8 (72)	4 (36)
Levodopa-Carbidopa	41 (13)	19 (46)	10 (24)

(Continued)

TABLE 1 (Continued)

	Total $n = 307$ (%)	De-prescribing suggested (%)	De-prescribing achieved (%)
Other anti-Parkinson's #	20 (6)	11 (55)	9 (45)
medicines for dementia ##	72 (23)	65 (90)	43 (59)
NSAIDs @	26 (8)	24 (92)	14 (53)
Paracetamol	10 (3)	1 (10)	1 (10)
Dipyrone	26 (8)	5 (19)	3 (11)
Tramadol	15 (5)	8 (53)	7 (46)
Pregabaline	11 (4)	6 (54)	7 (63)
Opioids	18 (6)	7† (38)	6 (33)
Oxybutynin	18 (6)	14 (77)	10 (55)
Trospium chloride	21 (7)	10 (47)	11 (52)
Dutasteride	29 (9)	6 (20)	9 (31)
Laxatives	112 (36)	3 (2)	20 (17)
Pentoxifylline	2	2 (100)	2 (100)
Steroids (Oral)	14 (5)	6 (42)	5 (35)
Steroid Inhalers	49 (16)	6 (12)	11 (22)
Bisphosphonates	71 (23)	37 (52)	25 (35)
Melatonin controlled release (Circadin)	12 (4)	1 (8)	3 (25)
Anti-allergic	23 (7)	2 (8)	4 (17)
Iron Preparations	48 (16)	32 (67)	15 (31)
Over the counter (OTC) compounds†			
Calcium supplements	132 (43)	23 (17)	42 (32)
Vitamin D	193 (63)	14 (7.2)	49 (25)
Vitamin B12	50 (16)	7 (14)	11 (22)
Folic Acid	47 (15)	11 (23)	19 (40)
Multi-vitamins	131 (43)	27 (21)	22 (17)

†The last five over the counter (OTC) vitamins and minerals were NOT included in the total drug count. *DOAC, Direct Oral Anticoagulants (Dabigatran, Apixaban, Rivaroxaban), **DPP4INH, Dipeptidyl peptidase-4 inhibitor (Sitagliptin, Vildagliptin), ***Z-drugs, non-benzodiazepine sleep inducers (Zolpidem, Zopiclone). ^Anti Vertigo drugs = Betahistine Dihydrochloride, Cinnarizine, Sulpiride. ^^SSRI, Selective Serotonin Reuptake Inhibitor; SNRI, Serotonin–Norepinephrine Reuptake Inhibitors. ^^^Other Anti-Epileptics = Levetiracetam, Lamotrigine, Primidone, Topiramate. #Other Anti-Parkinson's = Amantadine, Selegiline, Rasagiline Pramipexole. ##Anti-Alzheimer's = to "improve memory" (donepezil, memantine, galantamine, rivastigmine). @NSAIDs, Nonsteroidal anti-inflammatory drugs (Ibuprofen, diclofenac, indomethacin).

represented by very old people, with comorbidity, dementia, frailty/disability, and/or limited life expectancy. This population poses new challenges to the medical community such as the worldwide problem of inappropriate medication use and polypharmacy (IMUP). Most previous attempts to combat IMUP were unsuccessful in reducing its negative medical, nursing, and socioeconomic effects (3, 10, 11, 21, 22). This may be in part due to the fact that strategies employed to fight IMUP were based on a single-disease–single-drug model, which assumes that patients are largely homogeneous. This is incongruent with the reality of older populations where heterogeneity is the norm and where there is no longer a "natural clinical course of disease," owing to the inseparable co-mingling of multiple diseases with multiple drugs (1, 3, 21). Older people, particularly the VOCODFLEX group, deserve a different clinical approach as they present unique challenges.

The etiology of IMUP is multifactorial. Older people are excluded from randomized controlled trials (RCTs) and the few trials in older people are non-representative of the general old population (23, 24). Therefore, applying all guidelines in older people may not necessarily lead to an improvement in the quality of care, and sometimes even cause greater harm than good (25). It may fuel vicious cycles of "prescription cascades" where symptoms resulting from IMUP are perceived as "new diseases," leading to futile evaluations and over-diagnosis (26), thus making the spread of IMUP inevitable.

There are many tools to assess the appropriateness of prescribing (27). However, even the most sophisticated computer-assisted methods (10) as well as lists of "drugs to avoid" (e.g., Beers criteria, START/STOPP) have failed to show significant improvements in clinical outcomes, rendering them insufficient as a standalone approach against IMUP (2, 3, 11). In our view, all these "drugs to avoid" approaches are basically flawed. Apart from an unbearable rate of false-positive alerts, separating "bad drugs" from "good drugs" may be dangerous, providing false reassurance to clinicians and concealing

TABLE 2 Prevalence of chronic diseases, geriatric syndromes/symptoms in the study (PDP) and control (NR) groups*

Chronic disease/ Syndrome	Total, *n* = 307	Non-responders NR, *N* = 161	Poly-de-prescribers PDP, *N* = 146	*p*
Hypothyroidism	69 (22.5)	42 (26)	27 (18.5)	0.111
Diabetes mellitus	119 (38.8)	70 (43.5)	49 (34)	0.075
Hyperlipidemia	236 (76.9)	127 (79)	109 (75)	0.381
Hypertension	246 (80.1)	136 (84.5)	110 (75)	**0.045**
Ischemic heart disease	94 (30.6)	50 (31)	44 (30)	0.862
Congestive heart failure	22 (7.2)	8 (5.0)	14 (10.0)	0.117
Atrial fibrillation	73 (23.8)	37 (23)	36 (25)	0.730
Peripheral vascular disease	23 (7.5)	12 (7.5)	11 (7.5)	0.979
Cerebral stroke	79 (26.0)	41 (25.5)	38 (26)	0.911
Chronic obstructive lung disease	37 (12.1)	22 (14)	15 (10)	0.362
Chronic renal failure	44 (14.3)	21 (13)	23 (16)	0.499
Benign prostatic hypertrophy	68 (22)	37 (23)	31 (21)	0.713
Urine incontinence	138 (45.0)	63 (39)	75 (51)	**0.031**
History of malignancy	62 (20.2)	29 (18)	33 (23)	0.317
Osteoporosis	135 (44)	68 (42)	67 (46)	0.519
Recurrent falls	193 (62.9)	96 (60)	97 (66)	0.217
Parkinson's disease (Parkinsonism)	41 (13.4)	21 (13)	20 (14)	0.866
Sleep disorders	233 (75.9)	123 (76)	110 (75)	0.826
Depression	149 (48.5)	71 (44)	78 (53)	0.103
Anxiety	91 (29.6)	48 (30)	43 (29.5)	0.945
Dementia	69 (22.5)	21 (13)	48 (33)	**<0.001**

*As written in the medical file, in brackets percentage (%) of group. Bold values are used to highlight statistical significance.

TABLE 3 Long-term objective end points of PDP (number of drugs, hospitalizations, and survival).

	Total *N* = 307	NR* *N* = 161	PDP* *N* = 146	*p*-value
Follow-up (months)	57 ± 30	58 ± 30	55 ± 29	0.319
No. of drugs at baseline	9.8 ± 2.6	10 ± 2.6	9.5 ± 2.5	0.021
No. of drugs suggested to de-prescribe	6.2 ± 2.1	6 ± 1.9	6.5 ± 2.3	0.021
No. of drugs for which de-prescribing was achieved	4.4 ± 3.1	2.2 ± 2.1	6.7 ± 2.0	<0.001
Rate of de-prescribing**	46% ± 30%	22% ± 19%	72% ± 14%	<0.001
Hospitalizations (*n* = 282)	117 (48.5%)	54 (44%)	63 (53%)	0.141
Deaths	188 (61%)	100 (62%)	88 (60%)	0.741
Survival rate after 3 years of follow-up (months)	73% ± 3.7%	73 ± 3.5%	73% ± 3.7%	0.940

*NR, Non-Responders; PDP, Poly de-prescribing study group. **Rate of de-prescribing = No. of Medications stopped at last visit/No. of Medications at baseline.

the damage caused by the interactions between the remaining, apparently "appropriate" drugs (19, 22).

In this study, we show that even "appropriate drugs" may become harmful when they accumulate in the system; stopping such "appropriate drugs" may contribute to the overall improvement achieved by PDP.

Gnjidic et al. (13) and Rausch et al. (14) have suggested that the number of different medications, starting from three or five, is associated with an increased likelihood of serious adverse drug effects (ADE). If the sum of all negative outcomes of polypharmacy (sometimes unrecognized) outweighs the potential benefits gained from every specific drug, then PDP can be the first step toward implementing the dictum "first, do not harm."

Our study represents the first longitudinal observational study in older people with polypharmacy, evaluating the effect of de-prescribing on long-term clinical outcomes and QoL.

The Garfinkel method we employed for de-prescribing has already been implemented in nursing departments (20) and in community-dwelling elders (1, 19) and exhibited safety and efficacy while achieving sustained improvements in clinical outcomes in both. In

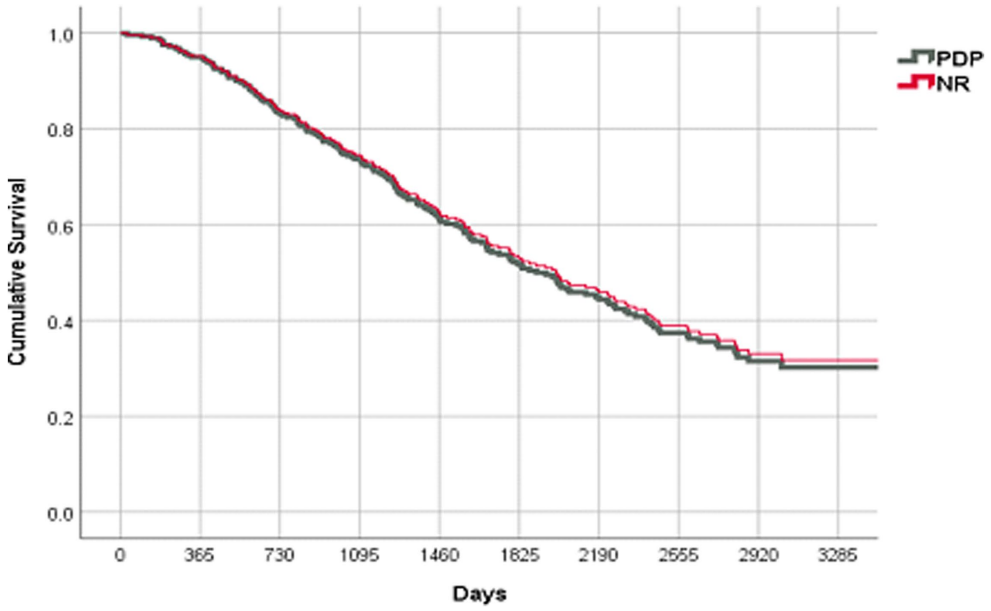

FIGURE 2
Survival curves: PDP vs. control groups.

this research, participants who best complied with de-prescribing and stopped more than 50% of their medications represented the study group (PDP). The non-responders (NR) group included patients who continued taking medications as before or more of them, or discontinued less than 50% of their initial drugs. Unlike our previous research where we used a cutoff of three medications to compare two groups, in this study, we chose to look at the percentage of drugs de-prescribed rather than the absolute number of medications. This may seem confusing because by achieving significant de-prescribing of nine drugs, a patient may still be classified among the non-responder, control group if the number of drugs taken in the first place was more than 18. We chose 50% as a cutoff between the two groups in order to check whether we really need to reduce a substantial amount of medications in order to observe any beneficial effect. We found that regardless of the number of drugs consumed, de-prescribing as many medications as possible (PDP) is beneficial.

When isolating all other factors, we showed in this study that the family doctor's willingness to follow through with de-prescribing recommendations was the most influential factor ($p < 0.001$) on the decision of the patient/family if and to what extent to adopt de-prescribing. The GP actually determined the patient's group (PDP or NR) and the consequences of this choice on the patient's clinical outcomes (Table 4).

The finding that in most cases where PDP is implemented improvement appears quickly—within 3 months following PDP with no worsening even after 2 years of follow-up—is encouraging. Combined with the prompt positive impact, the long-term benefits, such as sustained improvement over several years, highlight the enduring positive effects of PDP. Many times, patients/families themselves wish to broaden the spectrum of PDP, which highlights yet another beneficial medico-legal advantage of this method. All these enablers should help overcome common barriers that underlie patient's and doctor's fear of routine de-prescribing (12, 28).

The goal of stopping as many drugs as possible simultaneously does not include medications that are "life-saving" or improve QoL in specific subpopulations to which the patient belongs. As life expectancy decreases particularly in the VOCODFLEX population, the role of preventative drugs and the positive benefit/risk ratio of most medications is declining (29–31). Indeed, in our study, mortality rate was not increased even after years following PDP.

Most physicians are reluctant to de-prescribe "simultaneously" and prefer stopping drugs one by one. This reaction is rooted in our traditional "single-drug model" perception. However, the "one drug at a time" approach is inappropriate for the practice of de-prescribing. Facing "multi-disease multi-drug" situations, the risk of IMUP is increasing in correlation to the number of drugs. It is the combination of many drugs that result in the negative effects of IMUP, and this study shows that removing the largest possible combinations bestows the greatest benefit. Furthermore, as Holmes and others state, we may not have time to stop drugs one by one facing the unknown but limited life expectancy of these patients (30, 31).

In our perception, it is not important to know what drug combinations that were removed caused an improvement in each patient. The important issue is that we have successfully achieved the main goals of medicine: symptomatic improvement, better QoL, and patient/family satisfaction.

Strengths and limitations

This study is the first longitudinal research evaluating the long-term beneficial effects of poly-de-prescribing in terms of the extent of clinical benefits and improvement in the quality of life of older people in polypharmacy.

An important limitation of this study is the lack of randomization and a true "traditional" control group. The cohort

TABLE 4 Long-term subjective end points of Poly-de-prescribing (adjusted to PPS)†.

A. Comparison of specific clinical outcomes between groups						
	Total *N* = 282 (%)	NR *N* = 142 (%)	PDP* *N* = 140 (%)	NR*	PDP* OR (95% C.I.)	*p*-value
High patient satisfaction with medical change	182 (59)	57 (35)	125 (86)	1.0	9.5 (4.95–18.4)	<0.001
Health status improved	103 (34)	41 (26)	62 (42)	1.0	2.19 (1.27–3.77)	0.001
Functional status improved	51 (18)	16 (11)	35 (25)	1.0	2.43 (1.21–4.87)	0.012
Cognitive status improved	22 (7.5)	9 (6.3)	13 (9)	1.0	3.32 (1.93–5.71)	<0.001
Mental status improved	116 (41)	39 (27.5)	77 (55)	1.0	1.23 (0.47–3.19)	0.672
Nighttime sleep quality improved	86 (30.5)	25 (17.5)	61 (43)	1.0	3.38 (1.88–6.09)	<0.001
Daytime wakefulness improved	50 (18)	13 (9)	37 (26)	1.0	2.98 (1.44–6.15)	0.003
Urine continence improved	10 (3)	2 (1.4)	8 (5.7)	1.0	1.46 (0.54–3.96)	0.461
Appetite improved	58 (21)	23 (16)	35 (25)	1.0	5.43 (1.02–29.03)	0.048
Pain decreased	20 (7)	9 (6)	11 (8)	1.0	1.41 (0.79–2.80)	0.221

B. Comparison of initiation, length, and extent of clinical improvement**						
	Total *N* = 282 (%)	NR* *N* = 142 (%)	PDP* *N* = 140 (%)	NR	PDP OR (95% C.I.)	*p*-value
Improvement within 3 months	148 (52.5)	49 (34.5)	99 (71)	1.0	4.33 (2.51–7.46)	<0.001
Improvement persisted for more than 1 Year	146 (52)	49 (35)	97 (70)	1.0	3.92 (2.29–6.73)	<0.001
No worsening after 2 Years	166 (60)	67 (48)	99 (72)	1.0	2.36 (1.37–4.06)	0.002
Family doctor response accepted completely***	155 (55)	43 (30)	112 (80)	1.0	7.54 (4.24–13.39)	<0.001

†Full questionnaires could not be obtained from 25 participants. Therefore, the findings in this table are based on data from 282 participants only. *NR, Non-Responders; PDP, Poly de-prescribing study group. **Improvement = Improved + much improved on the 5-point Likert scale (see Methods, follow up). ***The Family Doctor accepted all recommendations for de-prescribing.

represents a group of people who were already dissatisfied by their current health situation and treatment and who chose to consult the geriatrician for a second opinion. This cohort therefore represents a self-selected target group, which may have influenced the impact of the PDP. All participants received recommendations based on the same algorithm, but compliance varied among them. A "pure" RCT would require de-prescribing many drugs and comparing outcomes in patients who did not have the same drugs removed. Considering the complexity of old patients' characteristics and limited life expectancy, performing a true RCT would be unrealistic. However, this preliminary "proof of concept" observational cohort study may serve as a basis for planning future randomized PDP studies.

Our "subjective results" (Tables 3, 4) are based on participants' opinion of how general health and specific conditions may have changed. The study could benefit from objective measures for clinical outcomes. Rather than using patient/family opinion for measuring subjective parameters, it would probably be better to use instruments that assess the overall quality of life (or components thereof) at both time points, not only at baseline before the intervention but also at a specified later time point (last follow-up). On the other hand, the fact that objective parameters showed no significant differences between the groups, while subjective parameters exhibited notable improvements in the PDP group, suggests that patient-reported outcomes and satisfaction play a crucial role in assessing the effectiveness of PDP. The lack of statistical significance in mental status improvement between groups in multivariate analysis warrants further investigation using larger samples.

Another limitation is that adverse symptoms such as falls have not been evaluated as outcomes and compared between the two groups.

One may argue that study participants might have had social desirability bias to report improved outcomes in the survey questionnaires. However, as all the participants responded to the same questionnaire, we do not believe this could result in a major

bias in the study. Another limitation to consider is that all the participants consulted the same geriatrician, making it difficult to distinguish between the benefit of the algorithm and the impact of the geriatrician's skill. This aspect could be of interest to others who may wish to replicate this work. Therefore, one should be cautious in deducing our results to the entire elderly population. The assertion that the clinical harm outweighs all beneficial effects without distinguishing between different types of medications and their potential individual impacts may be overly generalized. It is essential to recognize that not all drugs contribute equally to harm, and certain medications may exert distinct influences on clinical outcomes. The consideration of factors such as drug interactions, patient adherence, and individual characteristics may provide a better understanding.

For many older people including VOCODFLEX, poly-de-prescribing is a key clinical priority to prevent further morbidity/mortality. Routine drug re-evaluation is an essential part of CGA (32); the Garfinkel Algorithm should therefore be perceived not as a new intervention but rather an improved "medication debridement" tool, that should be used in a rational, guided, yet aggressive way (19, 20). This algorithm also adopts the 2012 recommendations of the Institute of Medicine (33): "Focus on QoL outcome measures, take a more coordinated approach to meeting both health and social needs", highlighting the shift in emphasis to 'living well' rather than reducing mortality (34). PDP wouldn't be necessary if periodic medication reviews were performed and medications stopped when necessary. Furthermore, we should change our "all drugs forever" attitude and educate all health professionals (35) as well as the general population (36, 37) stressing that every prescription should be viewed as a time-limited intervention. In line with many studies showing the negative health outcomes of IMUP, Fabbietti et al. (38) have proven that "Hyperpolypharmacy" is associated with functional decline. At the moment we can't offer supporting evidence or rationale for these findings but in the future, in order to enhance this hypothesis it would be crucial to elucidate the mechanisms through which the absolute number of drugs contributes to IMUP. Nevertheless, it may be concluded that deprescribing in itself is usually associated with a significant clinical economical win-win situation (39).

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, and further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by ethics committees: Shoham Medical Geriatric Center, Pardes Hana, Israel & Wolfson Medical Center, Holon, Israel. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because both ethics committees determined that an unwritten consent was sufficient (approval given by all participants or legal guardians).

Author contributions

DG: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Supervision, Validation, Writing – original draft, Writing – review & editing. YL: Data curation, Formal analysis, Investigation, Software, Supervision, Validation, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2024.1365751/full#supplementary-material

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Evaluating sarcopenia prevalence and SARC-F effectiveness in elderly Spanish women with RA: a comparative study of EWGSOP criteria

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Introduction: The European Working Group on Sarcopenia in Older People (EWGSOP) has put forward two key proposals for diagnosing sarcopenia: the EWGSOP1 in 2010 and the EWGSOP2 in 2019. These proposals are currently the most widely used guidelines for diagnosing sarcopenia. However, data on the prevalence of sarcopenia in patients with rheumatoid arthritis (RA) based on EWGSOP criteria are limited. This study aimed to: (a) establish the prevalence of sarcopenia in an elderly Spanish cohort of women with RA using both EWGSOP1 and EWGSOP2 criteria; and (b) evaluate the effectiveness of the SARC-F questionnaire in detecting sarcopenia.

Methods: In this observational, cross-sectional study, 67 women aged over 65 years who met the ACR 2010 criteria for RA were consecutively recruited from a tertiary university hospital. Assessments included: (a) demographic and anthropometric data; (b) RA-related variables (disease history, analytical evaluation, activity, disability, quality of life); and (c) sarcopenia-related variables (muscle strength, gait speed, skeletal muscle mass, and SARC-F questionnaire). The prevalence of sarcopenia was determined using both EWGSOP1 and EWGSOP2 criteria. Furthermore, the effectiveness of the SARC-F questionnaire for detecting sarcopenia were calculated.

Results: The prevalence of sarcopenia was 43% according to the EWGSOP1 criteria and 16% according to the EWGSOP2 criteria. Patients diagnosed with sarcopenia based on the latter criteria also met the EWGSOP1's criteria for sarcopenia. Agreement between the two sets of EWGSOP criteria was poor. The SARC-F questionnaire demonstrated an inherently high sensitivity (100%) as well as good specificity (75%) and diagnostic accuracy (79%) in detecting sarcopenia according to EWGSOP2 criteria.

Conclusions: The prevalence rate of sarcopenia among elderly Spanish women with RA varies significantly depending on whether EWGSOP1 or EWGSOP2 criteria are applied. The SARC-F questionnaire is effective for predicting sarcopenia when used in conjunction with the EWGSOP2 criteria, which is currently the most accepted standard in clinical practice.

KEYWORDS

sarcopenia, EWGSOP criteria, rheumatoid arthritis, elderly patients, SARC-F questionnaire, prevalence, muscle strength, diagnostic criteria

Introduction

Sarcopenia, a progressive and generalized skeletal muscle disorder characterized by the accelerated loss of muscle mass and function, is associated with increased adverse outcomes such as falls, functional decline, frailty, and mortality (1).

At present, there is no universally accepted operational definition of sarcopenia. However, the proposals published by the European Working Group on Sarcopenia in Older People (EWGSOP), first in 2010 (EWGSOP-1) (2) and subsequently in 2019 (EWGSOP-2) (3), remain the predominant criteria in use. These frameworks advocate for a sequential diagnostic strategy, despite employing different criteria (4). Specifically, EWGSOP-1 defines sarcopenia through the concurrent observation of low muscle mass and diminished muscle function, indicated by reduced muscle strength or compromised physical performance. In contrast, EWGSOP-2 defines sarcopenia by combining low muscle mass and strength, using physical performance evaluations to classify the severity of the condition. Furthermore, EWGSOP-2 recommends use of the SARC-F questionnaire (5) as a tool to identify individuals likely suffering from sarcopenia.

The diagnostic concordance between these two methodologies is recognized as minimal, which has led to disparities in the reported prevalence of sarcopenia, affecting both the general population (6) and individuals with specific conditions (7, 8).

Rheumatoid arthritis (RA), the most commonly diagnosed systemic autoimmune disease, is a complex rheumatic condition characterized by persistent, progressive articular and extra-articular manifestations, ultimately contributing to heightened disability and mortality rates (9, 10).

It is acknowledged that individuals with RA are at an elevated risk for developing sarcopenia compared to the general population (11). Nevertheless, the reported prevalence of sarcopenia among RA patients is highly variable, contingent on the diagnostic definition applied and the demographics of the study population (12).

This study aims to determine the prevalence of sarcopenia within a cohort of elderly Spanish women with RA, examining the application of both EWGSOP-1 and EWGSOP-2 diagnostic criteria. While EWGSOP-2 is the prevailing standard, comparing the two strategies may provide insights into the evolution of diagnostic practices and their potential implications for patient care. Additionally, this research seeks to evaluate the effectiveness of the SARC-F questionnaire in detecting sarcopenia within this demographic.

Materials and methods

Study population

This observational, cross-sectional study recruited women aged over 65 who met the ACR 2010 criteria for RA, as established during routine visits to the rheumatology service of a tertiary university hospital. We excluded patients with diseases that could significantly affect their condition, such as neoplasms, cardiac or respiratory insufficiency, and chronic liver or kidney disease.

All participants provided written consent, and the study received approval from the local ethics committee.

Study variables

Demographic and anthropometric data

- Age.
- Body mass index (BMI). BMI is the ratio of human body weight to squared height expressed in kg/m^2. It has been categorized as follows: $<$18.5 kg/m^2 is considered underweight; from 18.5 to 25 kg/m^2, normal range; from 25 to 30 mg/m^2, overweight; and $>$30 kg/m^2, obese.

RA assessment

- Evaluation of RA history: (a) disease duration; (b) current treatment (glucocorticoids, conventional disease-modifying antirheumatic drugs, biological disease-modifying antirheumatic drugs, Jak inhibitors); (c) rheumatoid factor seropositivity; and (d) positivity of anti-citrullinated peptides antibodies (ACPA).
- Analytical evaluation. We considered the following parameters: (a) erythrocyte sedimentation rate (ESR); (b) C-reactive protein (CRP); and (c) hemoglobin levels. The values corresponding to the last analytical study carried out were considered.
- Evaluation of RA activity. We used two indices: (a) the Disease Activity Score 28 (DAS28) and the Routine Assessment of Patient Index Data 3 (RAPID3).

  a) DAS28 (13) is a composite index of disease activity comprising tender and swollen joint counts in 28 joints, the Patient's Global Assessment of Disease Activity and the ESR. The higher the score, the higher the activity level. A value $<$2.6 suggests disease remission, a value between $\geq$2.6–$\leq$3.2 suggests low disease activity, a value $>$3.2–$\leq$5.1 suggests moderate disease activity and, finally, a value $>$5.1 suggests high disease activity.

  b) RAPID3 (14) is a validated index for measuring disease activity in patients with RA that includes three measures self-reported by the patient: pain, physical function, and global assessment of the disease. The higher the score, the higher the activity level. A value $\leq$3 suggests disease remission, a value between 3.01–6 suggests low disease activity, a value between 6.01–12 suggests moderate disease activity and a value $>$12 suggests high disease activity.

- Evaluation of disability. We used the Health Assessment Questionnaire (HAQ) (15). This questionnaire assesses physical functioning as difficulty performing daily living activities; the score ranges from 0 to 3. The higher the score, the higher the disability level.
- Evaluation of health-related quality-of-life. We used the SF-12 questionnaire (16), which consists of 12 questions that measure 8 health domains to assess physical and mental health. Physical health-related domains include general health, physical functioning, physical role, and body pain. Mental health-related

scales include vitality, social functioning, emotional role, and mental health. For each participant, we then calculated two summary scores using the SF-12—physical and mental health—utilizing the weighted means of the eight domains.

Sarcopenia assessment

Sarcopenia was assessed by two different methods: EWGSOP-1 and EWGSOP-2 criteria.

Muscle strength was evaluated with a calibrated handheld Jamar type dynamometer (Kern hand grip digital dynamometer 80K1). Two trials for each hand were performed and the best result from the strongest hand was used. The cutoffs points considered were <20 kg for the EWGSOP-1 criteria and <16 kg for the EWGSOP-2 criteria.

Gait speed, measured in meters/second (m/s), was evaluated by the 6-m gait test, where the participant walked along a straight 6-meter track and the time was measured with a stopwatch. The cutoffs points considered were <0.8 m/s, both in the EWGSOP-1 and EWGSOP-2 criteria.

Muscle mass was assessed by calculating the Skeletal Mass Index (SMI). SMI is established by the following formula: appendicular skeletal muscle mass/height^2. The examinations were made with a densitometer Hologic Horizon W (Hologic Inc., Bedford, MA), recording fat and lean mass in the arms, trunk, and legs. The patient is placed supine, centered on the table with arms stretched to the sides of the body, hands facing the legs without touching them and the thumbs upwards. The cutoff point in both criteria is a value $\leq$5.67 kg/m^2.

As required by the EWGSOP-2 criteria, the SARC-F (5) was applied as a screening tool for sarcopenia. It includes five components: strength, assistance walking, rising from a chair, climbing stairs, and history of falls. The score ranges from 0 to 10. Cutoff value of $\geq$4 suggest the presence of sarcopenia and indicate the need for further evaluation.

According to the EWGSOP-1 criteria, sarcopenia is considered when a patient presents low muscle mass with low muscle strength or poor physical performance. According to the EWGSOP-2 criteria, sarcopenia is considered possible when a patient presents low muscle strength and low muscle mass. Sarcopenia is considered severe, according to the EWGSOP-1 criteria, when a patient presents any anomaly in the three components analyzed (low muscle mass, low muscle strength, and poor physical performance). Sarcopenia is considered severe, according to the EWGSOP-2 criteria, when a patient with sarcopenia additionally presents poor physical performance.

EWGSOP-2 includes the category of "probable sarcopenia" when a patient presents low muscle strength with normal muscle mass.

Statistical analysis

We calculated the necessary sample size based on a 4.5% expected prevalence of sarcopenia in RA (12), using the formula: $n = Z^2 \times p \times (1\text{–}p)/E^2$. Here, Z is the Z-score for a 95% confidence level (1.96), p is the prevalence rate (0.045), and E is the margin of error (5%). The calculation yielded a sample size of 67 participants.

Data are presented as the mean plus or minus the standard deviation for continuous variables and as a number and percentage for categorical variables. Prevalence rates are given as percentages. Continuous variables were tested for normality using the Kolmogorov-Smirnov test. Differences among parametric variables were assessed using ANOVA; for non-parametric variables, we used the U-Mann-Whitney or Kruskal-Wallis tests, when indicated. Differences among categorical variables were evaluated by the chi-squared test.

We assessed the level of agreement between the classifications of sarcopenia according to the two different criteria through Cohen's kappa coefficient. Interpretations based on kappa values are as follows: <0: less agreement than would be expected by chance; $0 \leq k \leq 0.2$: slight agreement; $0.21 \leq k \leq 0.4$: fair agreement; $0.41 \leq k \leq 0.6$: moderate agreement; $0.61 \leq k \leq 0.8$: substantial agreement; $0.81 \leq k \leq 1$: almost perfect agreement.

We also conducted a comprehensive evaluation of the effectiveness and precision of SARC-F. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy were assessed. Sensitivity measures the proportion of true positive cases correctly identified by the test among all actual positive cases. Specificity assesses the test's ability to correctly identify negative cases among those without the studied condition. Positive Predictive Value (PPV) represents the probability that a positive test result is true. Negative Predictive Value (NPV) indicates the probability that a negative test result is true. Diagnostic accuracy reflects the proportion of true results, both positive and negative, in relation to the total results obtained.

Results

Our study included a total of 67 patients, as detailed in Table 1. According to the EWGSOP-1 criteria, 43.3% (29/67) of the patients were diagnosed with sarcopenia, and 7.5% (5/67) exhibited severe sarcopenia. Using the EWGSOP-2 criteria, the prevalence of sarcopenia was found to be lower at 16.4% (11/67), with severe sarcopenia observed in 6% (4/67) of the patients. Additionally, 26.9% (18/67) were classified with probable sarcopenia under EWGSOP-2 criteria.

All patients diagnosed with sarcopenia under EWGSOP-2 criteria also met the EWGSOP-1 criteria for sarcopenia. However, the agreement between the two sets of criteria was poor, as indicated by a Cohen's kappa coefficient of 0.409 ($p < 0.001$), demonstrating significant discrepancies in how each set of criteria categorizes sarcopenia.

The mean SARC-F questionnaire score among the cohort was 2.9 ± 1.9, with 62.7% (42/67) of patients scoring 4 or higher. Patients identified with sarcopenia by EWGSOP-2 criteria had a significantly higher mean SARC-F score of 5.1 ± 1.5, compared to 2.5 ± 1.6 for those without sarcopenia ($p < 0.001$).

The diagnostic performance of the SARC-F questionnaire is detailed in Table 2, showing its sensitivity, specificity, predictive values, and diagnostic accuracy for diagnosing sarcopenia using EWGSOP-2 criteria.

TABLE 1 Patient characteristics in accordance with the presence of sarcopenia based on the EWGSOP1 and EWGSOP2 criteria.

	All patients (n: 67)	EWGSOP1			EWGSOP2		
		Without sarcopenia (n: 38)	With sarcopenia (n: 29)	*p*	Without sarcopenia (n: 56)	With sarcopenia (n: 11)	*p*
Age (years)	72.6 ± 6.2	71.8 ± 5.0	73.7 ± 7.4	ns	72.6 ± 6.2	72.7 ± 6.2	ns
BMI (kg/m^2)	27.4 ± 4.8	29.6 ± 4.9	24.6 ± 2.9	<0.001	27.7 ± 5.1	26.1 ± 2.7	ns
Underweight (*n*, %)	0	0	0		0	0	
Normal range (*n*, %)	23 (34.3%)	8 (21.1%)	15 (51.7%)		19 (33.9%)	4 (36.4%)	
Overweight (*n*, %)	25 (37.3%)	11 (28.9%)	14 (48.3%)	<0.001	18 (32.1%)	7 (63.6%)	<0.05
Obese (*n*, %)	19 (28.4%)	19 (50%)	0		19 (34%)	0	
Disease duration (years)	17.9 ± 9.8	15.7 ± 9.8	20.6 ± 9.3	<0.05	16.8 ± 9.6	23.3 ± 9.9	<0.05
RF seropositivity (*n*, %)	40/57 (70.2%)	21/32 (65.6%)	19/25 (76%)	ns	32/48 (66.6%)	8/9 (88.8%)	ns
ACPA positive (*n*, %)	44/59 (74.6%)	26/34 (76.5%)	18/25 (72%)	ns	35/50 (70%)	9/9 (100%)	ns
ESR (mm/h)	22.6 ± 16.5	20.5 ± 14.4	25.3 ± 18.7	ns	21.6 ± 15.6	22.6 ± 16.5	ns
CRP (mg/dL)	4.9 ± 7.3	4.4 ± 6.7	5.6 ± 8	ns	4.3 ± 6	8.0 ± 12	ns
Hemoglobin (g/dL)	13.5 ± 10.2	13.8 ± 10.2	13.1 ± 8.8	<0.01	13.6 ± 9.8	12.8 ± 10	<0.05
DAS28	2.8 ± 1.0	2.6 ± 1	3 ± 0.98	ns	2.7 ± 1	3 ± 0.9	ns
Remission (*n*, %)	29 (43.3%)	20 (52.6%)	9 (31%)		26 (46.4%)	3 (27.3%)	
Low disease activity (*n*,%)	21 (31.3%)	10 (26,3)	11 (37,9)		16 (28.6%)	5 (46.4%)	
Moderate disease activity (*n*,%)	16 (23.9%)	8 (21.1%)	8 (27.6%)	ns	13 (23.2%)	3 (27.3%)	ns
High disease activity (*n*, %)	1 (1.5%)	0	1 (3.5%)		1/56 (1.8%)	0	
RAPID3	9.6 ± 7.5	9.4 ± 7.8	9.7 ± 7.2	ns	8.6 ± 7.2	14.3 ± 7.2	<0.05
Remission (*n*, %)	20/64 (31.2%)	12/35 (34.3%)	8 (27.6%)		18/53(34%)	2 (18.2%)	
Low disease activity (*n*, %)	3/64 (4.7%)	1/35 (2.9%)	2 (6.9%)		3/53 (5.6%)	0	
Moderate disease activity (*n*, %)	19/64 (29.7%)	11/35 (31.4%)	8 (27.6%)	ns	18/53 (33.9%)	1 (9.1%)	<0.05
High disease activity (*n*, %)	22/64 (34.4%)	11/35 (31.4%)	11 (37.9%)		14/53 (26.5%)	8 (73.7%)	
HAQ	0.15 ± 0.34	0.10 ± 0.16	0.22 ± 0.48	ns	0.12 ± 0.32	0.29 ± 0.42	ns
SF-12							
Mental health	44.7 ± 11.4	46.4 ± 10.3	42.4 ± 12.6	ns	45.0 ± 11.2	43.6 ± 13.0	ns
Physical health	37.6 ± 9.3	37.6 ± 9.5	37.6 ± 9.1	ns	38.7 ± 9.2	30.9 ± 7.2	<0.05
Current medication							
Glucocorticoids (n,%)	31 (46.3%)	17 (44.7%)	14 (48.3%)		24 (42.8%)	7 (63.6%)	
cDMARDs (n,%)	56 (83.6%)	36 (94.7%)	23 (79.3%)		50 (89.3%)	9 (81.8%)	
bDMARDs (n, %)	27 (40.3%)	12 (31.6%)	15 (51.7%)	ns	22 (39.3%)	5 (45.5%)	ns
Jak inhibitors (n,%)	1 (1.5%)	0	1 (3.5%)		1(1.8%)	0	
SMI	5.48 ± 0.79	5.86 ± 0.64	4.97 ± 0.69	<0.001	5.61 ± 0.69	4.76 ± 0.93	<0.01
SMI ≤ 5.67 Kg/m^2 (*n*, %)	40 (59.7%)	11 (28.9%)	29 (100%)	<0.001	29 (51.8%)	11 (100%)	<0.01

(Continued)

TABLE 1 (Continued)

	All patients (n: 67)	EWGSOP1			EWGSOP2		
		Without sarcopenia (n: 38)	With sarcopenia (n: 29)	*p*	Without sarcopenia (n: 56)	With sarcopenia (n: 11)	*p*
Grip strength < 16 Kg (*n*, %)	40 (59.7%)	15 (39.5%)	25 (86,2%)	<0,001	29 (51.8%)	11 (100%)	<0.01
Gait speed <0.8 m/s (*n*, %)	53 (79.1%)	12 (31.6%)	9 (31%)	ns	17 (30.4%)	4 (36.4%)	ns

BMI, body mass index; RF, rheumatoid factor; ACPA, anti-citrullinated peptides antibodies; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; DAS28, Disease Activity Score 28; RAPID3, Routine Assessment of Patient Index Data 3; HAQ, Health Assessment Questionnaire; cDMARDs, conventional disease-modifying antirheumatic drugs; bDMARDs; biological disease-modifying antirheumatic drugs; SMI, Skeletal Mass Index. ns, not significant.

TABLE 2 Sensitivity and specificity of SARC-F with predictive values and diagnostic accuracy.

	Sensitivity	Specificity	PV+	PV−	Diagnostic accuracy
Sarcopenia by EWGSOP-2	100%	75%	44%	100%	79%
Low grip strength	45%	74%	72%	48%	57%
Low SMI	35%	59%	56%	38%	45%
Slow gait speed	57%	72%	48%	79%	67%

PV+, Positive Predictive Value; PV−, Negative Predictive Value.

Discussion

Recent advancements in RA treatment have markedly improved patient outcomes (17), enabling significant reductions in clinical symptoms, and even disease remission, by targeting inflammatory signals. Alongside the progress being made in managing RA activity, there's a growing recognition of associated comorbidities. Beyond traditional ones, conditions such as sarcopenia are now acknowledged as important considerations in clinical practice (18).

Sarcopenia, a condition marked by muscle loss, significantly impacts elderly patients by increasing the incidence of falls and hospitalization risks, reducing daily living activity capabilities, and elevating morbidity and mortality rates. Its prevalence among older populations notably contributes to frailty and disability, presenting substantial social and economic challenges (19).

Sarcopenia is traditionally classified into one of two categories: primary, attributed solely to aging; and secondary, stemming from other conditions like diseases or treatments. Though considered somewhat outdated, this classification system not only highlights sarcopenia's potential role as a symptom of underlying diseases (1), including cancer, liver, heart, endocrine, or kidney disorders, but also emphasizes its importance as a comorbidity.

RA-induced joint inflammation leads to pain, joint destruction, and reduced physical activity (10). Given that reduced physical activity and chronic inflammation are sarcopenia risk factors, assessing its prevalence in RA patients is pertinent.

Currently, sarcopenia is often undiagnosed, and while universal screening is impractical, a case-finding strategy (1) for opportunistic detection is recommended. This approach is crucial in patients with at higher risk of sarcopenia, such as in older adults or those with chronic diseases, as it will help identify and manage this condition more effectively.

It is well established (20) that the prevalence of sarcopenia in free-living older adults is lower when diagnosed according to EWGSOP-2 criteria vs. EWGSOP-1 criteria. To date, only three studies have compared these criteria in patients with specific diseases. Almeida et al. (7) analyzed both sets of criteria in 57 patients with non-alcoholic fatty liver disease (mean age: 52.7 ± 11.3 years; 75.4% females), finding sarcopenia in 3.5% of cases using only the EWGSOP-1 criteria. Valent et al. (8), studying 81 Parkinson's disease patients (mean age: 73.8 ± 5.3 years; 45% females), reported sarcopenia prevalences of 51.9% with EWGSOP-1 and 28.4% with EWGSOP-2. Lastly, de Freitas et al. (21) examined 242 patients with type 2 diabetes mellitus (mean age: 68.3 ± 5.6 years; 54% females), observing sarcopenia prevalences of 16.9% with EWGSOP-1 and 7% with EWGSOP-2.

We have established that, in the context of RA, the prevalence of sarcopenia significantly diverges depending on whether EWGSOP1 or EWGSOP2 criteria are applied, highlighting a marked discrepancy in agreement between these two diagnostic approaches. The question of whether this variance stems from an overestimation by EWGSOP1 or an underestimation by EWGSOP2 remains to be elucidated through longitudinal studies. Importantly, it must be noted that EWGSOP1 (2) prioritizes muscle mass as the principal diagnostic criterion, whereas

TABLE 3 Patient characteristics and prevalence of sarcopenia by EWGSOP-2 criteria in RA studies.

	Brance et al. (23)	Dietzel et al. (12)	Cano-Garcia et al. (24)	Present study
Number of patients	105	289	76	67
Age	53.3 ± 13.4	59.4 ± 11.3	71.0 ± 4.8	72.6 ± 6.2
Female sex	82.9%	80%	78.9%	100%
BMI	26.96 (23.4–29.9)	27.0 ± 4.5	28.1 ± 1.0	27.4 ± 4.8
Disease duration	6.0 (2.5–14)	9 (12)*	18 ± 7.8	17.9 ± 9.8
RF seropositivity	80.4%	79%	75%	70.2%
ACPA positive	ND	87%	72%	74.6%
DAS28	3.6 (2.8–5.0)	2.1 (1.3)*	2.9 ± 1.1	2.8 ± 1.0
HAQ	ND	0.5 (0–1.3)*	1.28 ± 0.79	0.15 ± 0.34
Glucocorticoids	62.9%	53%	57.9%	46.3%
cDMARDs	71.4%	68%	59.2%	83.6%
bDMARDs	28.6%	46%	73.7%	40.3%
Jak inhibitors	0	8%	0	1.5%
Prevalence of probable sarcopenia	ND	24.6%	46.1%	26.9%
Prevalence of confirmed sarcopenia	19%	4.5%	15.8%	16.4%
Prevalence of severe sarcopenia	6.9%	0	1.3%	6%

*The data are presented as the median (Interquartile Range, IQR). BMI, body mass index; RF, rheumatoid factor; ACPA, anti-citrullinated peptides antibodies; DAS28, Disease Activity Score 28; HAQ, Health Assessment Questionnaire; cDMARDs, conventional disease-modifying antirheumatic drugs; bDMARDs; biological disease-modifying antirheumatic drugs; ND: not done.

EWGSOP2 (3) shifts the focus toward low muscle strength as the primary diagnostic measure. Evidence suggests that muscle strength is a more reliable predictor of adverse health outcomes commonly associated with sarcopenia, including diminished quality of life, increased disability, and higher mortality rates in older populations residing in the community (22). This distinction underscores the need for a nuanced understanding of sarcopenia's diagnostic criteria and their implications for patient outcomes.

Furthermore, gender-specific factors and the severity of RA could have also played critical roles in influencing these prevalence rates. Women with RA often exhibit different clinical outcomes compared to men, which might be reflected in their sarcopenic status when assessed under varying diagnostic criteria. Moreover, the systemic inflammation associated with RA and its treatments can variably affect muscle strength and mass, potentially exacerbating sarcopenia under different diagnostic frameworks.

The data observed in this study has revealed a starker contrast between the two diagnostic tools than what has been reported in prior studies (7, 8, 21). Specifically, the prevalence of sarcopenia identified using EWGSOP-2 criteria was nearly one-third of that detected with EWGSOP-1 criteria. This pronounced difference may be attributed not only to potential disease-specific variations, but also to methodological differences in our approach compared to other studies. Unlike previous research that utilized Bioelectrical Impedance Analysis (BIA) for muscle mass assessment, our study employed Dual-Energy X-ray Absorptiometry (DXA), the gold standard technique for analyzing muscle mass. This methodological distinction likely contributes to the observed discrepancy in sarcopenia prevalence between the two sets of diagnostic criteria.

Information regarding the prevalence of sarcopenia in RA patients, as defined by any of the EWGSOP strategies, remains limited. Specifically, there is a lack of data concerning the frequency of this condition when applying the EWGSOP-1 criteria. Table 3 compiles the primary outcomes from studies published to date (12, 23, 24) that have assessed the prevalence of sarcopenia using the EWGSOP-2 criteria. The prevalence observed has been very close to that reported by Cano-Garcia et al. (24) among a cohort of 77 patients whose clinical and demographic characteristics closely align with those of the current series.

As anticipated, individuals diagnosed with sarcopenia according to both criteria exhibited lower SMI and grip strength. However, it was surprising to note that there were no significant differences in age or gait speed between the groups. Furthermore, while no marked differences were evident in most RA-specific variables, exceptions were noted in terms of disease duration and hemoglobin levels.

Our findings indicate the SARC-F screening questionnaire offers an inherently high sensitivity (100%), a sine qua non condition for diagnosis, as well as good specificity (75%) and diagnostic accuracy (79%) for identifying sarcopenia in RA patients when used alongside the EWGSOP-2 criteria. However, SARC-F is not a good indicator of altered grip strength, SMI or gait speed. Then, in our cohort, the predictive power or SARC-F for decreased muscle strength, mass, and function is notably

low. It is conceivable that structural damage associated with RA may introduce a confounding variable, potentially impacting its predictive accuracy.

In healthcare practice, the SARC-F questionnaire seems useful as a screening tool for the presence of sarcopenia in elderly female patients with RA. From an operational perspective, its administration combined with the determination of muscle strength, would help to identify patients with RA who are at risk of developing sarcopenia, eligible to start a multidisciplinary program to prevent it.

The present study has several limitations: (a) its cross-sectional design precludes establishing causality between RA characteristics or evolution and the presence of sarcopenia; (b) it exclusively involved elderly women, since it focused on the group most at risk for sarcopenia; and (c) it was localized to a single center, though it is believed to reflect typical characteristics of established RA patients.

Moreover, the sample size was determined using the best available prevalence at the time the study was planned, which was 4.5% for sarcopenia in individuals with RA (12). However, the study found an observed prevalence of 16.4%, significantly exceeding expectations. This significant discrepancy suggests that the sample size may have been too small to achieve optimal statistical power and precision, considering the actual variability within the study population.

Considering all these limitations, caution must be exercised in generalizing findings. Indeed, broader, longitudinal studies are needed to confirm these observations and extend them to a more diverse population. Future studies should also consider recalculating the necessary sample size using this newly observed prevalence to enhance the robustness of the findings.

Nevertheless, it makes significant contributions to the field by comparing EWGSOP-1 and EWGSOP-2 criteria for screening sarcopenia in an elderly female RA cohort, thus constituting a novel approach in this area. Additionally, it evaluates the SARC-F questionnaire's effectiveness in detecting sarcopenia among RA patients, an aspect not previously explored.

Conclusion

This study, conducted among elderly Spanish women with RA, highlights that the detected prevalence rates of sarcopenia significantly differ based on the application of EWGSOP1 or EWGSOP2 criteria. Moreover, the SARC-F questionnaire shows good effectivity for predicting sarcopenia following the EWGSOP2 criteria, currently the most widely accepted in clinical practice. This underscores the importance of selecting appropriate diagnostic strategies for sarcopenia in RA patients, which can impact both clinical outcomes and management strategies.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the IDIBELL Clinical Research Ethics Committee of Bellvitge. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

LV-M: Data curation, Formal analysis, Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing. CG-V: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Validation, Writing – original draft, Writing – review & editing. MM: Data curation, Investigation, Methodology, Software, Writing – original draft, Writing – review & editing. LB-A: Data curation, Investigation, Methodology, Software, Writing – original draft, Writing – review & editing. DB: Data curation, Formal analysis, Investigation, Methodology, Software, Writing – original draft, Writing – review & editing. JN: Data curation, Investigation, Methodology, Software, Writing – original draft, Writing – review & editing. XJ: Data curation, Investigation, Methodology, Software, Writing – original draft, Writing – review & editing. JMN: Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Frailty and Parkinson's disease: the role of diabetes mellitus

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Parkinson's disease (PD) is a chronic neurodegenerative disease associated with a progressive loss of dopaminergic neurons, clinically characterized by motor and non-motor signs. Frailty is a clinical condition of increased vulnerability and negative health outcomes due to the loss of multiple physiological reserves. Chronic hyperglycemia and insulin resistance, which characterize diabetes mellitus (DM), have been reported to alter dopaminergic activity, increase the risk of PD, and influence the development of frailty. Even though diabetes may facilitate the development of frailty in patients with PD, this relationship is not established and a revision of the current knowledge is necessary. Furthermore, the synergy between DM, PD, and frailty may drive clinical complexity, worse outcomes, and under-representation of these populations in the research. In this review, we aimed to discuss the role of diabetes in the development of frailty among patients with PD. We summarized the clinical characteristics and outcomes of patients with concomitant DM, PD, and frailty. Finally, interventions to prevent frailty in this population are discussed.

KEYWORDS

aging, frailty, diabetes mellitus, Parkinson's disease, insulin resistance, hyperglycemia

1 Introduction

Frailty and Parkinson's disease (PD) are conditions frequently associated with advancing age. Frailty is a disorder of several physiological systems that implies concerns related to vulnerability and negative outcomes. The overall prevalence of frailty and prefrailty in community-dwelling adults is, respectively, 17% (95% Confidence Interval [CI] 16–18%), and 45% (95% CI 44–46%) (1). Regardless of the definition of frailty, the prevalence of frailty in community-dwelling adults across increasing age groups is progressively high. In individuals aged 60–69 years, the prevalence is 16%; in 70–79 years, 20%; in 80–89 years, 31%; and in above 90 years, 51% (1). Considering the geographic region, physical frailty prevalence appears higher in Africa and lower in Europe: 22% vs. 8%. For women, physical frailty and prefrailty prevalence proportions are 15 and 49% compared with 11 and 45% for men (1). Fatigue, weight loss, gait impairment, fluctuating disability, and confusion are common clinical presentations of frailty.

The prevalence of PD rises steadily with age: 41 per 100.000 in 40–49 years; 107 per 100.000 in 50–59 years; 428 per 100.000 in 60–69 years; 1,087 per 100.000 in 70–79 years; and 1903 per 100.000 in older than 80 years (2). Differences in prevalence by geographic location have been reported: 1601 per 100.000 in individuals of 70 to 79 years of age from Europe, North America, and Australia, compared with 646 per 100.000 in individuals from Asia (2). Differences were found

for women and men of 50 to 59 years of age: 41 per 100.000 in women and 134 for 100.000 in men (2). PD is characterized by motor symptoms: bradykinesia, rigor, tremor, and postural instability. Cognitive decline, depression, sleep disorders, orthostatic hypotension, and gastrointestinal disorders are cardinal non-motor symptoms and conditions associated with PD. Hoen and Yahr (HY) scale is a clinical rating scale used to categorizing patients affected by PD. HY scale includes five stages and describes important aspects of motor involvement, compromised balance, physical independence, and disability (3). The Unified Parkinson Disease Rating Scale (UPDRS) and its modified version: Movement Disorder Society-Unified Parkinson Disease Rating Scale (MDS-UPDRS) is a comprehensive tool utilized for the quantification of PD severity and progression (4). The MDS-UPDRS covers non-motor and motor aspects of daily living, motor examination, and motor complications.

Progressive loss of dopaminergic neurons and impairment of serotoninergic signaling are considered cardinal pathways in the pathophysiology of PD (5, 6). Of note, chronic hyperglycemia and insulin resistance have been reported to alter dopaminergic activity and influence the onset of PD (7, 8). Indeed, experimental and clinical evidences have underlined common pathophysiology mechanisms between diabetes mellitus (DM) and PD (9). DM is common among the elderly, accounting for a prevalence rate of up to 30% (10). Age-dependent modification of body composition and age-related insulin resistance may influence the high incidence rate of DM among the elderly (10, 11). In addition, longitudinal studies underline that diabetes is an important factor in the progression of frailty (12, 13). Reasonably, the decline of motor functions and the onset of neuropsychiatric conditions, which characterize PD, influence the development of vulnerability and progression to frailty. It should be mentioned that frailty assessment models include diabetes as part of the deficits necessary for frailty detection. The presence of DM in studies that focus on the relationship between PD and frailty is not rare (14, 15). Even though diabetes may facilitate the development of frailty in patients with PD, this relationship is not established and a revision of the current knowledge is necessary. Furthermore, the synergy between DM, PD, and frailty may drive clinical complexity, worse outcomes, and under-representation of these populations in the research. In this review, we aimed to discuss the role of diabetes in the development of frailty among patients with PD. We summarized the clinical characteristics and outcomes of patients with concomitant DM, PD, and frailty. Finally, interventions to prevent frailty in this population are discussed.

Considering the aim of this review, an article search was performed on MEDLINE/PubMed using a combination of the following free text terms and major medical subject headings: "Frailty," "Parkinson's Disease," and "Diabetes Mellitus." We searched articles published until November 2023. Additional articles were also identified by the reference list of studies included in this review. We reviewed studies that evaluated physical and or multidimensional frailty in patients with PD and diabetes. Both experimental and clinical studies on the relationship between PD and diabetes, diabetes, and frailty were also considered for this review. Our search was limited to articles published in the English language.

2 The concept of frailty

Frailty has been defined as a geriatric syndrome, characterized by multidimensional loss of physiological reserves, vulnerability toward stressor events, and negative health outcomes (16). Physical, cognitive, psychological, and social functioning are considered the main domains of frailty (17). Lower physical activity is associated with frailty and disability (18, 19), whereas higher physical activity levels resulted in 41% decreased odds of frailty (20). The incidence of frailty in individuals with malnutrition is 10.35 times higher (95% CI: 3.78–28.36) than the incidence of robustness (21). A significant association between an increased number of medications and frailty has been reported (22). Comorbidities such as dementia, heart failure, and cancers are characterized by a high prevalence of frailty (23–25). Disability, reduced quality of life, falls, fractures, delirium, hospitalizations, need for long-term care, and death are negative outcomes of frailty. It has been suggested that chronic inflammation, activation of the immune system, age-related modification of the endocrine system, and nervous and cardiorespiratory systems are important factors for the development of frailty (26, 27).

Several frailty assessment tools have been described in the present literature (28). However, quantification of frailty is based on the frailty phenotype (FP) model, frailty index (FI) derived by accumulative deficits and comprehensive geriatric assessments (CGA). Fried's FP is a physical frailty model and one of the most common frailty models applied as a prognostic tool. Unintentional weight loss of 4.5 kg or more during the last year, low handgrip strength, self-reported exhaustion, slow walking speed, and low physical activity are criteria of Fried's FP, and the presence of three or more of them identifies frailty (29). The presence of one or two of these criteria classifies individuals in prefrail. Although a widely accepted definition of prefrailty is lacking, it has been suggested that prefrailty is a multifactorial, multidimensional, and dynamic syndrome (30). Prefrailty should be considered as a transitional and reversible state before the onset of frailty. The clinical manifestations of prefrailty are weakness, fatigue, or no symptoms.

FI based on accumulative deficits incorporates symptoms, signs, disabilities, and comorbidities (31). This model is computed by the number of health deficits divided by the total number of the variables screened. A higher number of health deficits identifies greater frailty. FI derived from comprehensive geriatric assessment includes functional, nutritional, cognitive, and psychological assessments and is highly associated with FI based on accumulative deficits (32). The Clinical Frailty Scale (31), the Edmonton Frailty Scale (33), the Study of Osteoporotic Fractures Frailty Index (34), the Tilburg Frailty Indicator (35), and the Multidimensional Prognostic Index (36) are other frailty measurement tools, which originate from the main frailty models and have been validated in different populations and clinical settings. Despite different frailty measurements having different accuracy (37, 38) the ability of frailty models in the prediction of adverse clinical outcomes has been well established (36).

Even though the impact of frailty on health outcomes is strong, frailty is not routinely measured in clinical practice. Clinical assessment of frailty status tends to be evaluated by the perception of clinicians of patient frailty, the experience of clinicians, and self-perception of patients. It has been reported that objective measurement of frailty results in different to perception of health providers and or self-perception (39, 40). Anyhow, a potential relationship between the perception of frailty and survival has been described (41).

3 Frailty and Parkinson's disease

Approximately 38% of patients with PD are identified as frail by the FP model (42). The occurrence of frailty among patients with PD compared to patients without PD resulted higher in different studies: 69.4% vs. 24.2% (43) and 35.6% vs. 5.2% (44). A longitudinal study including patients with newly diagnosed PD concluded that the presence of PD increased frailty risk: odds ratio (OR) =6.68; 95% CI (3.15–15.62) (15). It should be mentioned that patients with PD compared to controls are characterized by a higher number of comorbidities and polytherapy (45). Furthermore, sarcopenia is common, and it is associated with disease severity in PD (44, 46). PD may trigger the development of frailty, but a bidirectional relationship is also possible. Frail patients, identified with either Fried's FP or FI, had approximately 4- to 12-fold higher odds of having a diagnosis of PD diagnosis and 2.8 to 8.3 higher odds of prodromal PD (47). Furthermore, a recent prospective cohort study concluded that prefrailty and frailty were associated with incident PD, independent of genetic background, comorbidities, sociodemographic factors, and lifestyle (48).

Frailty has been associated with longer PD duration: 16.5 ± 8.5 years in frails vs. 9.6 ± 6.3 years in non-frail patients ($p < 0.001$) (44). Data from several studies report that frail patients compared to non-frail patients present a significantly higher Hoehn and Yahr Scale, indicating a more advanced stage. For instance, the Hoehn and Yahr Scale in frail vs. non-frail patients resulted: 3.3 ± 0.9 vs. 2.0 ± 0.8, $p < 0.001$ (44); 2.17 ± 1.12 vs. 1.54 ± 1.02, $p < 0.009$ (49); 2.5 ± 0.9 vs. 1.5 ± 0.6, $p < 0.001$ (50). Frailty has been associated with significantly higher scores in MDS-UPDRS part I-IV (44, 50). UPDRS parts II and III were significantly different in patients with idiopathic PD (50). Postural instability and gait disorder were more common among frail patients with PD, while tremor dominant subtype less frequent (44, 50). In contrast, a recent study observed that frail patients were characterized by a higher risk of rest tremor, facial bradykinesia, overall bradykinesia, and rigidity (47). Higher doses of levodopa therapy have been described among frail patients (44, 49, 50), and frailty is independently associated with higher levodopa doses (50).

Short-term memory, attention, visuospatial function, and executive function were significantly worse in frail patients with PD (49). Cognitive performance evaluated by Montreal Cognitive Assessment (MoCA) resulted in significant differences among frail patients with PD compared to non-frail patients: 22.6 ± 4.2 vs. 27.5 ± 2.5 ($p < 0.001$) (50). In line with these results, other studies also describe an increased risk for cognitive decline and dementia (15, 44, 51). The relationship between cognitive decline and frailty remained significant even after adjustment for potential confounders such as age, gender, PD duration, and therapy (50).

The Geriatric Depression Scale was significantly associated with frailty in patients with PD, regardless of the gravity of movement disorders (52). In line with these results, another study reported an independent association between depression and frailty in a group of patients with PD (53). In addition, disability was a significant characteristic of patients with concomitant PD and frailty. Reduced quality of life has been reported as a characteristic of frail patients with PD (44, 54, 55). However, a pilot observation study did not find a significant effect of frailty on the quality of life among PD patients, indicating that more research is necessary in this field (56). Furthermore, both self-perception of physical and mental health were related to postural control and impacted the quality of life (57). Self-perceived weakness in patients with PD without demonstrable weakness in neurological examinations was associated with fatigue, which is one of the characteristics of prefrailty (58). Self-perceived quality of mobility correlated with cerebellum hyper-metabolism and frontal hypo-metabolism as demonstrated by PET imaging, suggesting that perception of impaired quality of mobility may have a neurophysiological basis related to both motor and non-motor manifestations in PD (59).

Regarding the impact of frailty on survival, different studies have described that frail patients with PD present higher odds of in-hospital mortality and reduced overall 1-year survival (60–62). Furthermore, frail patients presented a higher risk of other adverse events such as falls, delirium, and hospitalizations (62).

4 Diabetes mellitus and Parkinson's disease

The relationship between diabetes and PD has been explored by a considerable number of experimental and clinical studies. An experimental model of early type 2 DM induced by high-fat diet revealed impairment of nigrostriatal dopamine function and increased iron deposition in substantia nigra (63). Accumulation of α-synuclein and neuroinflammation were aggravated in the midbrain of type 2 DM, suggesting that metabolic inflammation exacerbates degeneration of neuronal dopamine (64). Furthermore, insulin resistance mediated the activation of reactive oxygen species (ROS), mitochondrial dysfunction, and increased α-synuclein in dopaminergic neurons (65). It has demonstrated that chronic upregulation of IL-1β and IL-18 leads to increased insulin levels, which may be important for DM development (66). In addition, alpha-synuclein deposition activates NLRP3 inflammasome via cathepsin B signaling, which, in turn, may enhance PD development (67). Recently, it has been described that the adrenergic system in specific β2-adrenergic receptors (β2AR) modulates the transcription of α-synuclein and use of β2AR agonists, such as salbutamol was associated with reduced risk of PD development (68). Of interest, experimental models have revealed that β2AR signaling regulates pancreatic β-cell insulin secretion, and silencing of the β2AR or pharmacological treatment with β_2AR antagonist resulted in glucose response impairment. Therefore, it can be hypothesized that the implication of β2AR signaling in DM may modulate the expression of α-synuclein and trigger the development of PD.

Several clinical studies have highlighted an increased risk of PD in patients with DM (69–72). In a previous meta-analysis study, we reported that the prevalence of DM among PD patients is approximately 10% and diabetic patients suffer from a higher risk of developing PD: OR = 1.34; 95% (CI 1.26–1.43 $p < 0.0001$) (73). Furthermore, pre-diabetes increased the odds of subsequent PD and this association was more accentuated among young individuals and the female population (74). Increased glycated hemoglobin (HbA1c) levels were associated with neuroaxonal damage and cognitive impairment among patients with PD (75). However, the association of diabetes and PD is not supported by all studies. A large prospective study did not provide evidence for any relationship between baseline diabetes and risk of PD (76) and a meta-analysis study of case–control studies suggested that diabetic patients may have a decreased incidence of PD (77). It should be mentioned that the heterogeneity in cross-sectional, case–control, and cohort studies focusing on the

relationship of PD and DM is high. These discrepancies may be explained also by the interaction of demographic characteristics such as age and gender. Indeed, we identified age as an important moderator of the prevalence of diabetes among PD (73). Another factor as increased medical surveillance in diabetic patients, the effect of diabetes on cardiovascular mortality, and anti-hyperglycemic agents may influence the PD-DM relationship (78). It has been reported that in patients with concomitant PD and DM, worse postural symptoms balance impairment, and faster motor progression are present (79, 80). Furthermore, diabetic patients with PD have a faster cognitive decline and impairment of attention, working memory, and frontal executive function (81, 82).

Insulin pre-treatment showed a protective effect against cell toxicity induced by 1-methyl-4-phenyl pyridinium used in PD experimental models. Insulin also ameliorated insulin signaling pathways in dopaminergic neurons (83). Intranasal treatment with insulin provided protective effects on dopaminergic neurons in a rat model of PD, in parallel with improvement in motor activity and behavior (84).

In clinical studies, a single dose of intranasal insulin increased the resting-state functional connectivity between the default multiple network and hippocampal regions in older adults with type 2 DM (85). Another study demonstrated that in diabetic patients, intranasal insulin enhanced vasodilatation in the insular cortex, which regulates task performance related to attention (86). In persons with Alzheimer's disease, intranasal insulin administration did not show effects on cognitive and functional performance over a period of 12 months (87). However, data from a pilot longitudinal study report that in PD, intranasal insulin administration may improve functional motor skills and may preserve cognitive performance (88).

The incident rate of PD in a cohort of metformin exposure was 5.9 cases per 1,000 patients per year, compared to 2.43 cases per 1,000 patients per year in the group without metformin exposure. More than 4 years of metformin exposure was associated with a lower risk of PD: adjusted HR = 0.04; (95% CI 0.00 to 0.37) (89). In contrast, a recent analysis concluded that metformin use was associated with a significantly increased risk of PD incidence OR = 1.66, (95% CI 1.14–2.42), compared with non-metformin users or glitazone therapy (90). In a Taiwanese population cohort, sulfonylureas increased the risk of PD by 57%, and combination with metformin use avoided this effect (91). Overall, a meta-analysis study did not find any change in the risk of PD related to sulfonylurea administration: HR: 1.13 95% CI: 0.96–1.32 (92). An inverse association between the use of thiazolidinediones and an incidence of PD, with an HR of 0.74 (95% CI, 0.59–0.92) has been described (93) and another observation found a slight reduction of PD risk (94). However, a nationwide population-based study did not find a beneficial role (72).

Preclinical studies have reported that glucagon-like peptide-1 receptor (GLP1R) agonists improved dopamine levels and reduced neuronal damage through the modification of oxidative stress and inhibition of inflammatory cytokines (95). A preliminary data analysis reported that diabetic patients treated with GLP1R agonists had a significant improvement at 12 months on the MDS-UPDRS of 2.7 points, compared with a mean decline of 2.2 points in control patients ($p = 0.037$) (96). A significantly reduced rate on the onset of PD and use of GLP1R agonists has been also described as incidence rate ratio (IRR) =0.38 (95% CI 0.17–0.60; $p < 0.01$) (97). However, results from another study did not show a significant association (94), and the response to therapy was worse in elderly patients with DM longer than 10 years (98). For the first time, a nationwide case–control study reported that the use of dipeptidyl peptidase-4 (DPP4) inhibitors was associated with a decreased risk of PD: OR = 0.23 (95% CI 0.07–0.74) (99). Strong evidence of an inverse association between the use of DPP4 inhibitors and the incidence of PD was described by another study IRR = 0.64; (95% CI 0.43–0.88; $p < 0.01$). Finally, a meta-analysis of studies reporting data on (DPP4-i) reveals that DPP4 inhibitors use was associated with reduced risk of PD: HR:0.69 95%CI:0.56–0.86 (92).

Modification of insulin secretion in pancreatic cells after levodopa therapy has been described in a rodent model (100). Furthermore, bromocriptine, a dopamine agonist, improved glycemic control and reduced insulin requirement in type 2 DM subjects on high-dose insulin therapy (101). Meta-analysis of randomized controlled trials found that dopamine agonists improve glycemic control in diabetic patients without serious adverse events (102). A large primary care-based national observational study observed that the incidence of diabetes in patients with PD occurred less frequently: OR = 0.53 (95% CI 0.33–0.87). The odds of developing diabetes in patients with PD and levodopa therapy were higher compared to patients without PD and levodopa therapy: OR = 0.22 (95% CI 0.10–0.48) (103).

5 Diabetes mellitus and frailty

Frailty and DM share common pathological mechanisms. Age-dependent reduction in skeletal muscle mass, sarcopenia, and increased visceral adiposity is associated with insulin resistance (104, 105). Oxidative stress, mitochondrial dysfunction, and chronic inflammation are other mechanisms linked to both frailty and diabetes (10).

Analysis adjusted for potential age, gender, and other confounding risk factors resulted in a consistent association between DM and frailty prevalence (106). DM has also been associated with a lower likelihood in the improvement of frailty status (107). Hyperglycemia has been associated with the development of frailty. Furthermore, a U-shaped relationship between glycemia and frailty has been described where glycemia levels <8.8 mmol/L and > 10 mmol/L were associated with an increased risk of frailty (108). Hypoglycemia and glycemic decompensation were associated with multidimensional impairment in the elderly with DM (109). However, a recent study found that out-of-range glucose concentration, defined also as dysglycemia, is significantly associated with incremental frailty, and hyperglycemia was predictive of mortality explainable by frailty (110). It has been reported that patients with higher Hb1Ac at baseline developed worse frailty status during 10 years of follow-up (111). However, another study did not find a U-shaped relationship between frailty and HbA1c level, suggesting that good glycemic control might be more important for frailty than poor glycemic control in patients with DM (112).

Patients with DM and frailty, regardless of methods used to quantify or measure frailty, are characterized by an increased risk of overall mortality compared to non-frail patients with DM (106).

Diabetic patients are characterized by a high risk of fractures despite normal or increased bone mineral density (113). Of interest, a prospective cohort study revealed a significant relationship between the risk of incident fragility fractures and frailty: HR of 1.02 (95% CI 1.01–1.03) (114).

Cardiovascular, cancer-related, and all-cause mortality were higher among middle-aged adults with DM. Furthermore, falls, major cardiovascular events, and hypoglycemia were also significantly related to the presence of frailty (115). Of note, in frail diabetic and hypertensive patients, a significant interaction between physical and cognitive domains has been described (116). Evaluations of cognitive status and physical performance with 5-min walking speed test would be useful for the elderly with DM or other cardiovascular risk factors. Furthermore, insulin resistance was a significant and independent predictor of cognitive performance in prediabetic frail patients (117). Considering the strict correlation between physical and cognitive performance the concept of cognitive frailty has been proposed, cognitive frailty has been defined as the coexistence of physical frailty and cognitive impairment in the absence of other neurological diseases and/or Alzheimer's disease (118).

A recent study reported that cognitive frailty is common among diabetic patients. Age, duration of diabetes, intellectual activity, albumin levels, calf circumference, and depressive state were identified as independent risk factors (119). Furthermore, closer attention to the elderly who have poor self-care ability and low income has been suggested as early indicators of cognitive frailty in diabetic patients (120).

Management of elderly people with DM is complex as a consequence of multimorbidity, polytherapy, and complications related to adverse drug events and hypoglycemia. Recent consensus statements on the management of elderly with type 2 DM indicate frailty assessment as a component of the clinical management and modification of glycemia targets. Therapeutic choices should be tailored to vulnerability and frailty status (121). An HbA1c target of 64–69 mmol/mol is indicated in patients with severe frailty and reduced life expectancy (122).

It has been suggested that metformin may be a potential pharmacological intervention that modifies the trajectories of frailty (123). Even though only intensive lifestyle interventions reduced frailty prevalence among frail diabetic patients and metformin use was not associated with significant reduction (124), administration of extended-release metformin in frail women with concomitant diabetes and hypertension ameliorated cognitive performance (125). In line with this finding, during a 4-year follow-up study, metformin use was associated with a reduction of frailty risk (126).

Frailty was associated with a significantly lower probability of initiating therapy with a GLP-1 receptor agonist and an SGLT2 inhibitor than non-frail diabetic people (127). Empagliflozin reduces frailty in diabetic and hypertensive patients, most likely by reducing mitochondrial Ca2+ overload and reactive oxygen species (128). Recently, another study concluded that GLP1R agonists and SGLT2 inhibitors safely improved cardiovascular outcomes and all-cause mortality, with higher benefits among frail patients (129).

6 Frailty and Parkinson's disease: the potential role of diabetes mellitus

A case–control study that included patients with a diagnosis of DM prior to PD showed that diabetic patients with PD require higher doses of levodopa treatment and experience more severe PD symptoms (129). Other studies have described that higher doses of levodopa were associated with frailty, regardless of the model used for frailty assessment (44, 50, 53). In contrast, another study reported that the median annual levodopa equivalent dose increased initially in the non-frail (400 mg/day) and prefrail groups (439 mg/day). Levodopa equivalent dose declined progressively in the mildly frail 400 mg/day, moderately frail (334 mg/day), and severely frail (304 mg/day) groups (61). The relationship between frailty and drug therapy is bidirectional, and medication review is necessary for the frail patients, and therefore, underestimation of the levodopa–frailty relationship may be influenced by dose modifications. Diabetic patients with PD, compared to non-diabetic patients with PD, differed significantly regarding cognitive performance, behavioral and mood disorders, and activities of daily living. In addition, motor examination showed worse outcomes in patients with DM compared to patients not affected by DM (129). Prospective studies focused on the relationship between incident frailty and depressive symptomatology provide evidence for increased bidirectional risk (130). Depression occurs in approximately 25–50% of patients affected by PD. Chronic inflammation and increased cortisol levels may lead to insulin resistance and impairment of the hypothalamic–pituitary–adrenal axis (131). Furthermore, depression, cognitive decline, and motor symptoms resulted in significant predictors of impaired activities of daily living and the development of dependency among patients with PD (132). Another case–control study found that diabetic patients with PD are characterized by increased postural instability and motor feature severity. Postural instability persisted even after controlling for hypertension and BMI. These clinical features were not explained by differences in striatal dopaminergic denervation, leukoaraiosis, or large-fiber polyneuropathy (133). Postural instability determines a greater risk of developing prefrailty and frailty among the elderly (134). Gait impairment, beyond gait speed, could help identifying different categories of frailty. It has been suggested that gait variability might reflect a multidimensional reduction and may be useful in identifying frailty (135).

Progression in the severity of UPDRS part III motor signs such as gait impairment and bradykinesia together with a significant overall cognitive decline have been associated with diabetes in PD patients (136, 137). While this study did not observe differences in specific memory domains across PD patients with and without DM, another study (136) underlined that frontal executive functions and attention were impaired in this population (81). Impairment in executive functions resulted in an independent risk factor for the development of physical frailty in patients with PD. Executive functions coordinated by the prefrontal cortex and subcortical areas are necessary to perform complex tasks or activities. Loss of the dopaminergic neurons and a disconnected hippocampus, amygdala, and prefrontal cortex may influence cognitive function, gait speed, and muscle mass loss.

Sarcopenia and PD share common characteristics (138). Patients with PD are characterized by poor physical performance and lower physical activity compared to healthy population. Poor nutritional status, modification in body composition, and hormonal axis alternations may influence the development of sarcopenia in PD. Furthermore, degeneration of the motor neuron units, reduction in the number of motoneurons, and modification of the gray matter have been suggested as possible mechanisms in patients with PD who have sarcopenia (139, 140). Finally, diabetic neuropathy may affect muscle strength and insulin resistance and chronic hyperglycemia may lead to a reduction in muscle mass and hand grip strength and physical performance (141). The relationship between DM PD and frailty is presented in Figure 1.

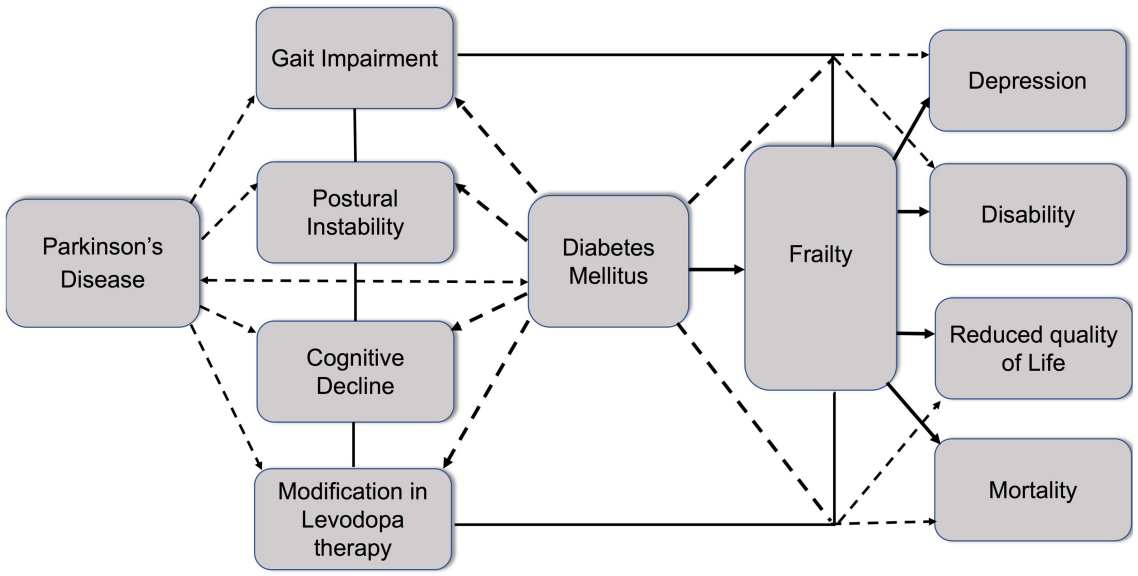

FIGURE 1
Schematic diagram highlighting the relationship between diabetes, Parkinson's disease, and frailty. Parkinson's disease (PD) is characterized by gait impairment, postural instability, and cognitive decline. Modification of levodopa therapy may be necessary during PD progression. Diabetes mellitus (DM) and PD share common pathomechanisms. Diabetes increases the risk of PD onset and aggravates symptoms such as gait impairment, postural instability, cognitive decline, and the need for modification in levodopa therapy. Moreover, diabetes contributes to the development of frailty in PD patients, leading to the enhancement of negative outcomes, including depression, disability, reduced quality of life, and increased mortality.

6.1 Interventions to prevent frailty among diabetic patients with Parkinson's disease

Implementation of routine assessments for the identification and stratification of frailty status is of great importance considering the overall negative impact on health outcomes. Early detection of prefrailty and or frailty in diabetic patients affected by PD would be necessary to develop specific and tailored interventions in order to reduce the disability and dependence burden. On the other side, screening for DM should be regular and accurately performed also in frail patients with PD.

Physical activity is considered a plausible protective factor for both DM and PD. Aerobic activity enhanced cognitive performance and stabilized the progression of PD in the corticostriatal sensorimotor network (142). Balance and strengthening training were not effective in reducing repeat falls across patients with PD, but balance and self-efficacy significantly improved. Furthermore, this intervention may be more beneficial among patients with moderate PD (143). However, another study found that after 10 weeks of exercise, the self-perceived fall risk improved only in severe PD (144).

Modest increments in moderate to vigorous physical activity had a clinically meaningful impact regarding cardiovascular risk factors and scores in diabetic patients (145). Future studies should evaluate the role of tailored training programs in diabetic patients with PD.

Several clinical investigations have reported that DPP4-i and GLP1R agonists were associated with reduced risk of PD (92, 96, 97) and also a beneficial role in frailty status have been associated with GLP1R agonists and sodium-glucose cotransporter 2 (SLGT2) inhibitors (128, 146). Indeed, experimental models reveal that treatment with dulaglutide, a GLP1R agonist, is protective against skeletal muscle injury by inhibiting inflammation and regulating the differentiation of myoblasts (147). A retrospective longitudinal analysis revealed that basal insulin co-therapy and GLP-1 receptor agonists may be effective in maintaining appendicular skeletal muscle mass (148). Future studies should investigate the role of antidiabetic agents not only in the prediction but also amelioration of frailty status among diabetic patients with PD.

7 Conclusion

The current evidence suggests that diabetic patients with PD have an increased risk for the development of frailty. Frail patients with concomitant PD and DM are characterized mostly by gait impairment, postural instability, sarcopenia, and cognitive decline. Dependency, depression, low quality of life, higher doses of levodopa therapy, and an overall negative health outcome may further characterize PD patients with DM. Early detection of vulnerability and frailty status and glycemic control in this population would be necessary for a better management of patients. Future research should explore the impact of interventions tailored to frailty aspects on health outcomes. Specific mechanisms of insulin resistance that contribute to frailty and the role of antidiabetic drugs on frailty among diabetic patients with PD should be investigated. Clinical trials should evaluate the role of antidiabetic drugs in the prevention and amelioration of frailty among diabetic patients with PD.

Author contributions

KK: Conceptualization, Writing – original draft, Writing – review & editing. AP: Writing – original draft, Writing – review & editing. LB: Writing – original draft, Writing – review & editing. GR: Writing – original draft, Writing – review & editing. GP: Writing – original draft, Writing – review & editing. GG: Writing – original draft, Writing – review & editing.

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Conflict of interest

GP is a full-time employee and a shareholder of F. Hoffmann-La Roche Ltd.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Association between SARC-F scores and risk of adverse outcomes in older patients with cardiovascular disease: a prospective study at a tertiary hospital in the south of Vietnam

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Introduction: Older patients typically face elevated mortality rates and greater medical resource utilization during hospitalizations compared to their younger counterparts. Sarcopenia, serving as a prognostic indicator, is related to disability, diminished quality of life, and increased mortality. The SARC-F questionnaire, known for its cost-effectiveness, offers a valuable means of assessing sarcopenia. This study aims to explore the association between SARC-F scores and risk of adverse outcomes in elderly patients with cardiovascular disease at a Ho Chi Minh City hospital.

Method: Participants aged 60 and above, admitted to the Department of Cardiology - Interventional and Cardiovascular Emergency of Thong Nhat Hospital in Ho Chi Minh City from November 2021 to June 2022, were recruited for the prospective, single-center study. The prognostic outcomes included all-cause death and the initial occurrence of emergency re-hospitalization within 6 months' post-discharge. The Kaplan–Meier analysis compared the overall survival rates between different SARC-F score groups.

Results: The study enrolled 285 patients with a median age of 74 (67, 81). During a 6-month follow-up period, there were 14 cases of mortality. A SARC-F score of 4 or higher was significantly associated with an increased risk of all-cause mortality, with HR of 2.02 (95% CI: 1.39–2.92, $p < 0.001$), and higher incidence of re-hospitalization events with RR of 1.66 (95% CI: 1.06 to 2.59, $p = 0.026$). Kaplan–Meier survival analysis indicated a notably higher mortality rate in the patients with high SARC-F scores ($p < 0.001$).

Conclusion: In elderly patients with cardiovascular disease, the SARC-F questionnaire could serve as a simple and cost-effective method for detecting mortality and the risk of re-hospitalization.

KEYWORDS

sarcopenia, SARC-F questionnaire, cardiovascular disease, mortality, Vietnam

Introduction

As the global population continues to age, the healthcare system faces increasing challenges in managing the health and well-being of older individuals (1). Older patients often experience higher mortality rates and require more extensive medical resources during hospitalizations compared to their younger counterparts (2, 3). Therefore, it becomes essential to identify prognostic markers that can effectively forecast outcomes in this vulnerable demographic. Doing so is vital for enhancing patient care quality and optimizing the allocation of healthcare resources.

Sarcopenia, a progressive systemic skeletal muscle disease, is recognized as a key prognostic factor for elderly patients (4). This condition is strongly associated with adverse outcomes in elderly patients, including onset of disability (5), quality of life decline (6), and mortality (7). Besides, cardiovascular disease (CVD), a leading cause of morbidity and mortality in the elderly population, is particularly concerning in relation to sarcopenia (8).

The SARC-F questionnaire, consisting of five questions, offers a simple and cost-effective method for assessing sarcopenia (9). Additionally, the SARC-F has demonstrated a significant correlation between motor function and overall prognosis in individuals with CVD (10). This makes the SARC-F a valuable tool for the early detection of sarcopenia and for evaluating motor function and prognosis in patients with CVD.

While the SARC-F questionnaire has shown promise in identifying sarcopenia (11, 12), studies exploring its association with short-term prognosis remain limited. Understanding the relationship between SARC-F scores and the risk of adverse events can provide valuable insights into the prognostic value of this screening tool. Moreover, such knowledge can aid healthcare professionals in identifying high-risk patients and implementing appropriate interventions to improve outcomes. In Vietnam, the burden of CVD is increasing among older adults due to factors such as sedentary lifestyles, unhealthy diets, and an aging population demographic. Specific challenges faced by elderly patients with CVD in Vietnam include limited access to specialized cardiovascular care and a lack of awareness about cardiovascular risk factors and preventive measures among both patients and healthcare providers. Moreover, such knowledge can aid healthcare professionals in identifying high-risk patients and implementing appropriate interventions to improve outcomes. Therefore, this study aims to investigate the association between SARC-F scores and total combined events, comprising both all-cause death and all-cause re-hospitalization within 6 months' post-discharge in elderly patients admitted to the Cardiovascular Department of a tertiary hospital in Ho Chi Minh City, Vietnam. By elucidating this association, the study seeks to provide valuable insights into optimizing care for elderly patients with CVD and improving their clinical outcomes in the Vietnamese healthcare context.

Materials and methods

Study design and participants

This prospective, single-center study comprised a cohort of 285 patients. The inclusion criteria for participant selection were individuals aged 60 years and above who were hospitalized at the Department of Cardiology - Interventional and Cardiovascular Emergency of Thong Nhat Hospital in Ho Chi Minh City from November 2021 to June 2022, including those discharged in this period. The exclusion criteria encompassed individuals with acute severe illness, those with a pacemaker implant, individuals incapable of completing the questionnaire and physical examination. Convenience sampling was employed for participant recruitment.

Ethical approval was obtained from the Ethical Committee of the University of Medicine and Pharmacy at Ho Chi Minh City (Number: 544/HĐĐĐ-ĐHYD, signed September 22, 2022). Informed consent was obtained from all participating individuals, and all research procedures were conducted in accordance with the relevant ethical guidelines and regulations.

Parameters

In this study, we collected demographic information, body mass index (BMI), comorbidities, and laboratory test results. BMI was classified according to the World Health Organization guidelines, categorizing individuals as underweight (BMI < 18.5 kg/m^2), normal weight (BMI 18.5–22.9 kg/m^2), overweight (BMI 23–24.9 kg/m^2), and obese (BMI ≥ 25.0 kg/m^2) (13). The presence of comorbidities, including hypertension, coronary disease, heart failure, dyslipidemia, and diabetes, was identified either through diagnoses from specialists or extracted from patients' medical records. Smoking was defined as either currently smoking or having quit within the past year. For assessing kidney function, the estimated glomerular filtration rate (eGFR) was calculated using the Cockcroft – Gault equation (14).

Acquisition of SARC-F

Upon admission, patients underwent evaluation using the SARC-F questionnaire. This assessment involved interviewing for five key elements: strength, assistance in walking, ability to rise from a chair, capacity to climb stairs, and frequency of falls. Each component of the SARC-F was scored on a scale of 0 to 2 points, resulting in a cumulative score ranging from 0 to 10 points, with 0 representing optimal physical performance and 10 indicating the poorest. Strength was measured by asking, "How much difficulty do you have in lifting and carrying 10 pounds?" (None = 0; Some = 1; A lot or unable = 2). Assistance in walking was assessed by questioning, "How much difficulty do you have walking across a room?" (None = 0; Some = 1; A lot, use aids, or unable = 2). The ability to rise from a chair was determined by, "How much difficulty do you have transferring from a chair or bed?" (None = 0; Some = 1; A lot or unable without help = 2). Climbing stairs was evaluated by, "How much difficulty do you have climbing a flight of 10 stairs?" (None = 0; Some = 1; A lot or unable = 2). Falls were assessed by, "How many times have you fallen in the past year?" (None = 0; 1–3 falls = 1; 4 falls = 2) (9). Patients with a total score of 4 or higher were classified as having sarcopenia (9).

Prognostic outcomes

The prognostic outcomes in this study were established as a composite endpoint, encompassing all-cause mortality and the first

occurrence of re-hospitalization. The assessment of patient prognoses was conducted over 6 months' post-discharge. The duration until reaching the composite endpoint was determined by calculating the number of days from the patient's discharge to the occurrence of the events, whether it be all-cause death or re-hospitalization.

Statistical analysis

Categorical variables were described using frequencies and percentages (n (%)), while continuous variables were presented as mean with standard deviation (mean ± SD) or median with interquartile range (median (IQR)) according to the type of variables. To compare overall survival rates between two groups distinguished by the optimal SARC-F cut-off point for mortality prediction, Kaplan–Meier survival analysis alongside log-rank tests was employed. A multivariate analysis was conducted to identify factors influencing mortality, adjusting for age, existing morbidities, and nutritional status. Additionally, separate multivariate analyses were performed for each component of the SARC-F questionnaire to pinpoint specific items that significantly influence mortality. All statistical analyses were carried out using SPSS version 21 (IBM Japan, Tokyo, Japan), and a p-value of less than 0.05 was considered statistically significant.

Results

Demographic of study population

This research enrolled 285 participants aged 60 and above who completed the SARC-F questionnaire. Out of the total participants, 87 individuals (30.5%) were classified as having sarcopenia, indicated by a SARC-F score of 4 points or higher. The baseline characteristics of the study population is provided in Table 1. The cohort comprised 48.4% male and 51.6% female patients. The analysis revealed that those in the sarcopenia group were significantly older and women exhibited a higher prevalence of sarcopenia compared to men ($p < 0.001$). The participants' average BMI was 22.8 ± 3.33 kg/m^2, and nearly half of them (48.8%) were classified as overweight. Among the 285 patients, a high prevalence of hypertension was observed, with 88.1%, while 56.1% had coronary artery disease, and 22.1% suffered from heart failure. The cohort observed considerable rates of dyslipidemia and diabetes, with 57.9 and 40%, respectively. Additionally, a higher proportion of patients in the sarcopenia group had been diagnosed with heart failure (34.5% vs. 16.7%, $p = 0.001$) and had a greater prevalence of diabetes (50.6% vs. 35.4%, $p = 0.016$) than those in the normal group. Patients with sarcopenia had a higher rate of re-hospitalization within 6 months' post-discharge compared to the robust ones ($p = 0.001$). Furthemore, the percentage of patients who experienced all-cause death was higher in patients with sarcopenia than in those without sarcopenia ($p = 0.037$).

SARC-F scores distribution

Table 2 illustrates the distribution of SARC-F scores, highlighting pronounced disparities between patients with and without sarcopenia. In the aspect of strength, participants in the sarcopenia group faced notable challenges, whereas individuals in the non-sarcopenia groups experienced minimal or no strength difficulties. This trend extended to mobility, where the sarcopenia group demonstrated a higher dependency on walking assistance, unlike their non-sarcopenia counterparts. Similarly, the sarcopenia group encountered more pronounced difficulties in rising from a chair and climbing stairs compared to the non-sarcopenia group. Moreover, the incidence of falls was significantly higher in the sarcopenia group than in those without this condition ($p < 0{,}001$).

Mortality and re-hospitalization incidence

During the 6-month follow-up period, there were 14 events (4.91%) of all-cause mortality and 100 events (35.08%) of all-cause re-hospitalization among the study participants. The total combined events, comprising both all-cause death and all-cause re-hospitalization, were 114, resulting in an incidence rate of 0.8 events per person-year. The Kaplan–Meier survival curves (Figure 1) illustrated a notably poorer prognosis for patients in the sarcopenia group compared to the non-sarcopenia group ($\chi^2 = 15.73$; log-rank test, $p < 0.001$).

The univariate analysis revealed that the hazard ratio (HR) for all-cause death and re-hospitalization events in patients with SARC-F score ≥ 4 compared to those with SARC-F score < 4 was 2.02 (95% CI: 1.39–2.92, $p < 0.001$) in the unadjusted analysis (Table 3).

During multivariate regression, sarcopenia (SARC-$F \geq 4$), along with age, gender, diabetes, and heart failure, were included in the analysis. Notably, only sarcopenia indicated statistical significance. For individuals with SARC-F scores of 4 or higher compared to those with scores below 4, the HR is 1.66, with a 95% CI ranging from 1.06 to 2.59 (Table 4).

Discussion

This study aimed to investigate the association between SARC-F scores and mortality risk in elderly patients with cardiovascular disease. The results of this study revealed that a SARC-F score of ≥4 was significantly associated with a higher risk of all-cause death and re-hospitalization events in this population.

This study observed that the number of patients with CVD having SARC-$F \geq 4$ increased with age, was higher in females and in patients with heart failure or diabetes. The aging process encompasses various factors, such as natural declines in muscle mass and strength and increased inflammation, potentially contributing to the onset of sarcopenia (13). Besides, cardiovascular diseases, especially heart failure, may exacerbate the process of muscle loss (14). Chronic illnesses, especially CVD, can contribute to a state of systemic inflammation and metabolic changes that negatively affect muscle health (14). The combination of aging and the presence of CVD may induce or accelerate progression of sarcopenia. In addition, the most prominent pathway associated with sarcopenia and CVDs is insulin resistance. This phenomenon serves as a significant cardiovascular risk factor, independent of other risk factors, among older adults in community populations and individuals with diabetes (14). In a previous meta-analysis, Feng et al. (15) affirmed that sarcopenia was more prevalent in patients with diabetes. In accordance with our

TABLE 1 The baseline characteristics of patients.

Variable	Total ($n = 285$)	Sarcopenia (SARC-$F \geq 4$) $N = 87$	Nonsarcopenia (SARC-$F < 4$) $N = 198$	p-value
Age (years)	74 (67, 81)	79.49 ± 7.88	71 (64, 78)	**<0.001**
Female, *n* (%)	147 (51.6)	63 (72.4)	84 (42.4)	**<0.001**
BMI (kg/m^2)	22.8 ± 3.33	22.34 ± 3.21	22.95 ± 3.37	0.164
< 18.5	25 (8.8)	9 (10.3)	16 (8.1)	0.298
18.5–22.9	121 (42.5)	42 (48.3)	79 (39.9)	
23–24.9	71 (24.9)	21 (24.1)	50 (25.3)	
≥ 25.0	68 (23.8)	15 (17.3)	53 (26.7)	
Comorbidities				
Hypertension, *n* (%)	251 (88.1)	76 (87.4)	175 (88.4)	0.805
Coronary disease, *n* (%)	160 (56.1)	43 (49.4)	117 (59.1)	0.130
Heart failure, *n* (%)	63 (22.1)	30 (34.5)	33 (16.7)	**0.001**
Dyslipidemia, *n* (%)	165 (57.9)	45 (51.7)	120 (60.6)	0.162
Diabetes, *n* (%)	114 (40.0)	44 (50.6)	70 (35.4)	**0.016**
CKD, *n* (%)	36 (12.6)	12 (13.8)	24 (12.1)	0.696
Current smoking, *n* (%)	34 (11.9)	4 (4.6)	30 (15.2)	**0.010**
eGFR	72.3 (63.7–80.8)	72.3 (63.7–81.2)	72.3 (63.7–80.8)	0.661
All-cause re-hospitalization, *n* (%)	103 (36.1)	44 (50.6)	59 (29.8)	**0.001**
All-cause death, *n* (%)	14 (4.9)	8 (9.2)	6 (3.0)	**0.037**

BMI, Body mass index, CKD, Chronic kidney disease, *n*, Number. Significant p-values are presented in bold.

finding, Kitamura et al. (16) recorded that sarcopenia was more common in women with CVD.

Our study revealed a significant correlation between higher SARC-F scores and the presence of comorbidities. Certain comorbidities, such as diabetes, coronary heart disease, and vision problems, were identified as predictors of lower muscle strength in individuals aged 50 and older (17). Additionally, muscle mass and strength have been linked to elevated levels of inflammatory markers in patients with chronic diseases (13). Angulo et al. (18) found that multimorbidity at baseline was associated with a higher risk of sarcopenia during a twelve-year follow-up. Similarly, a systematic review by Pacifico et al. reported that individuals with dementia, diabetes, and respiratory diseases had a notably higher prevalence of sarcopenia compared to those without these conditions (19). Sarcopenia shares many risk factors with CVD, dementia, diabetes, and respiratory disease, such as sedentary behavior, low physical activity, inflammation, malnutrition, and various other mechanisms. This shared risk profile may explain the higher prevalence of sarcopenia in individuals with these age-related diseases (19). Consequently, there is a critical need to raise awareness and implement preventative strategies targeting both sarcopenia and its associated comorbidities.

Our findings suggest that a SARC-F score of 4 or higher is a predictor of a worse prognosis, including readmission or mortality post-discharge, in patients with CVD compared to those in the non-sarcopenia group (a score below 4). The identification of sarcopenia using the algorithm proposed by the European Working Group on Sarcopenia in Older People (EWGSOP), Yang et al. reported that this situation was associated with mortality during hospital stay and 1-year post-discharge among hospitalized older adults (7). A previous study by Ueshima et al. (20), a SARC-$F \geq 4$ score was a predictor of death within 30 days of hospitalization. Takumi Noda et al. found that sarcopenia assessment using the SARC-F was associated with increased in-hospital mortality in older patients, as well as heightened short-term mortality in individuals with CVD (11). Sarcopenia diminishes both muscle mass and strength, potentially impairing balance and increasing the risk of falls, consequently increasing the likelihood of hospitalization (21). The reduced activity and prolonged bed rest associated with hospital stays can further exacerbate muscle mass and strength, worsening functional

TABLE 2 SARC-F score details.

Variable	Total (n = 285)	Sarcopenia (SARC-F ≥ 4) (n = 87)	Non-sarcopenia (SARC-F < 4) (n = 198)	p-value
Strength				
None (0)	185 (64.9)	12 (64.9)	173 (87.4)	**<0.001**
Some (1)	33 (11.6)	17 (11.6)	16 (8.1)	
A lot or unable (2)	67 (23.5)	58 (23.5)	9 (4.5)	
Assistance in walking				
None (0)	199 (69.8)	13 (14.9)	186 (93.9)	**<0.001**
Some (1)	76 (26.7)	64 (73.6)	12 (6.1)	
A lot or unable (2)	10 (3.5)	10 (11.5)	0 (0.0)	
Rise from a chair				
None (0)	211 (74.0)	26 (29.9)	185 (93.4)	**<0.001**
Some (1)	66 (23.2)	53 (60.9)	13 (6.6)	
A lot or unable (2)	8 (2.8)	8 (9.2)	0 (0.0)	
Climb stairs				
None (0)	106 (37.2)	2 (2.3)	104 (52.5)	**<0.001**
Some (1)	98 (34.4)	20 (23.0)	78 (39.4)	
A lot or unable (2)	81 (28.4)	65 (74.7)	16 (8.1)	
Falls				
None (0)	246 (86.3)	62 (71.3)	184 (92.9)	**<0.001**
Some (1)	34 (11.9)	20 (23.0)	14 (7.1)	
A lot or unable (2)	5 (1.8)	5 (5.7)	0 (0.0)	

Significant p-values are presented in bold.

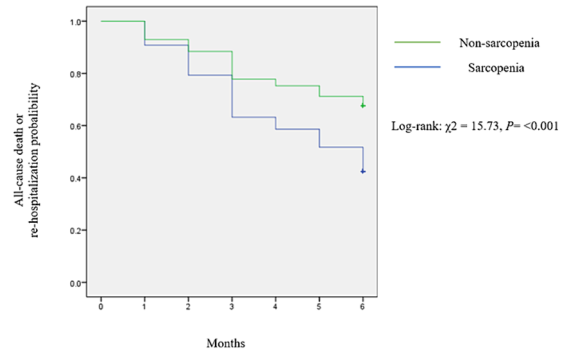

FIGURE 1
Kaplan–Meier curves illustrated all-cause death and all-cause re-hospitalization events stratified by SARC-F score.

deterioration and increasing the probability of post-discharge falls and readmissions (22). This perpetuating cycle of functional decline and re-hospitalization may contribute to mortality (22). In fact, the pathogenesis of sarcopenia and cardiovascular diseases (CVDs) involves a complex interaction of multiple factors, including malnutrition, physical inactivity, insulin resistance, inflammation, hormonal changes (14). CVDs can exacerbate the adverse outcomes of sarcopenia, such as falls, fractures, hospitalization, and mortality (14). Conversely, sarcopenia significantly contributes to adverse outcomes in older individuals with CVDs. For instance, in patients with coronary heart disease, sarcopenia could predict poor outcomes in elderly patients undergoing percutaneous coronary intervention (PCI). In a study involving 475 elderly patients with coronary artery disease who underwent successful PCI, sarcopenia was assessed by measuring the cross-sectional area of skeletal muscle at the first lumbar vertebra (L1) (23). The findings revealed that 29.7% of patients had a low L1 skeletal muscle index, which independently predicted all-cause mortality and major adverse cardiovascular events (23). Therefore, early identification and diagnosis of sarcopenia in primary care settings and hospitals are vital for initiating preventive or intervention strategies, thus mitigating the risks associated with sarcopenia and reducing the overall healthcare burden and expenses.

Sarcopenia is not merely a reduction in muscle mass but reveals significant implications for functional abilities. This study revealed an association between higher SARC-F scores and poorer functional outcomes. It suggests that individuals with sarcopenia may face challenges related to strength, mobility, and performing daily activities, indicating the importance of assessing this phenomenon clinically. In the African American Health (AAH) cohort, participants with SARC-F scores ≥4 exhibited slower chair stand times and weaker grip strength (5). Similarly, in the NHANES 1999–2006 survey, individuals with SARC-F scores ≥4 demonstrated slower walking times and weaker knee extension strength compared to the control group (5). These findings emphasize the clinical relevance of sarcopenia assessment and underscores the value of tools like SARC-F in recognizing and addressing this condition in elderly populations

TABLE 3 The hazard ratio for all-cause death and re-hospitalization in univariate analysis.

All-cause death and re-hospitalization events	HR	95% CI	*p*-value
SARC-F ≥ 4 (vs. SARC-F < 4)	2.02	1.39–2.92	<0.001

HR, Hazard ratio, CI, Confidence intervals.

TABLE 4 The hazard ratio for all-cause death and re-hospitalization in multivariate analysis.

All-cause death and re-hospitalization events	HR	95% CI	*p*-value
SARC-F ≥ 4 (vs. SARC-F < 4)	1.66	1.06–2.59	0.026
Age	1.02	0.99–1.04	0.193
Female	0.83	0.56–1.22	0.346
Diabetes	1.42	0.98–2.06	0.065
Heart failure	1.41	0.93–2.13	0.105

HR, Hazard ratio, CI, Confidence intervals.

and those with cardiovascular disease. By identifying individuals at risk of sarcopenia and understanding its impact on functional abilities, healthcare providers can implement appropriate interventions to improve outcomes and quality of life for these individuals.

It is worth noting that this study has some limitations. Firstly, the study was conducted at a single tertiary hospital, which may limit the generalizability of the findings to other settings. Secondly, the responses to the SARC-F questionnaire by some patients may have been influenced by undetected, subtle, transient cognitive impairments associated with their acute condition. Thirdly, the exclusion criteria applied, including acute severe illness and pacemaker implantation, may have inadvertently excluded certain relevant patient populations. Furthermore, the study did not extensively consider potential confounding factors that could influence the association between SARC-F scores and adverse outcomes, such as medication use, socioeconomic status, cognitive function, nutritional status and lifestyle habits. Finally, the study lacked a control group of younger individuals for comparison of SARC-*F* values between older and younger subjects.

Despite such limitations, the study addresses a gap in the context of dementia and its risk factors among Vietnamese people. This study has major strengths by addressing a gap in the literature regarding the role of the SARC-F questionnaire for predicting risk of adverse outcomes among Vietnamese elderly patients with cardiovascular disease. The study by Shinya Tanaka et al. has indicated that combining physical function measures with the SARC-F questionnaire might enhance predictive accuracy in elderly patients with CVD upon admission. This combined approach did not result in a statistically significant difference when compared to using the SARC-F questionnaire alone (24). These findings suggest that in clinical settings where time constraints limit the feasibility of conducting extensive physical function assessments, the SARC-F questionnaire should be a recommended and practical tool for prognostic evaluation among this patient population.

The study's findings have important clinical implications. Findings from the study sheds light on the prognostic value of the SARC-F questionnaire in identifying elderly patients at risk of adverse outcomes in the cardiovascular setting. In the context of geriatric cardiovascular care, the study emphasizes the need for comprehensive geriatric assessment tools, such as the SARC-F questionnaire, to identify vulnerable patients who may benefit from tailored interventions and closer monitoring. The SARC-F questionnaire can be easily administered in a clinical setting, making it a valuable tool for identifying elderly CVD patients at a higher risk of adverse outcomes. Early identification of these high-risk patients can help healthcare providers implement appropriate interventions and strategies to improve patient outcomes and reduce the burden of re-hospitalization. Integrating sarcopenia screening into routine cardiovascular evaluations can enhance risk stratification and guide personalized treatment strategies aimed at optimizing outcomes in older adults with cardiovascular conditions. Moreover, raising awareness among healthcare providers about the importance of assessing sarcopenia in elderly patients with cardiovascular disease could facilitate early identification and intervention.

Future prospective studies employing more age groups, larger sample sizes, and a comprehensive panel of risk factors in a multi-center clinical trial can provide further insights into the predictive utility of SARC-F for adverse outcomes in the elderly.

Conclusion

Among elderly patients with CVD, the SARC-F questionnaire is a valuable tool for predicting mortality and the risk of re-hospitalization in elderly patients with cardiovascular disease. A SARC-F score of ≥4 was associated with a significantly higher risk of all-cause death and re-hospitalization. The SARC-F questionnaire offers a simple and cost-effective method for screening and prognostic evaluation in busy clinical settings. The study sheds light on the potential of the SARC-F questionnaire as a screening tool for predicting adverse outcomes in elderly patients with cardiovascular disease. Future multi-center trials with diverse age groups, larger samples, and comprehensive risk factor panels can provide deeper insights into SARC-F's predictive value for adverse outcomes in older adults.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Ethical Committee of the University of Medicine and Pharmacy at Ho Chi Minh City (Number: 544/HĐĐĐ-ĐHYD, signed September 22, 2022). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

TaN: Conceptualization, Writing – original draft, Writing – review & editing, Data curation, Investigation, Project administration, Software, Validation. TN (2nd author): Conceptualization, Investigation, Software, Writing – original draft, Writing – review & editing. HC: Data curation, Methodology, Writing – original draft, Writing – review & editing. TN (4th author): Supervision, Writing – original draft, Writing – review & editing. TrN: Formal analysis, Project administration, Writing – original draft, Writing – review & editing. DD: Project administration, Validation, Writing – original draft, Writing – review & editing. TL: Validation, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Effects of multicomponent exercise nursing intervention in elderly stroke patients with frailty: a randomized controlled trial

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This study examines how multicomponent exercise nursing interventions affect the state of frailty, daily activities, and quality of life in elderly stroke patients with frailty. A total of 125 elderly stroke patients with frailty were randomly assigned to either a control group ($n = 62$) or an intervention group ($n = 63$). The control group received standard nursing care, while the intervention group received a multicomponent exercise nursing intervention in addition to standard care. Patients were assessed using the FRAIL Frailty Scale, Modified Barthel Index (MBI), and Short Form Health Survey (SF-36) before the intervention, 4 weeks after the intervention, and 12 weeks after the intervention. Significant differences were observed between the two groups in terms of frailty status, activities of daily living, and quality of life ($p < 0.05$). The intervention group had lower scores on the FRAIL Frailty Scale and higher scores on the MBI and SF-36 compared to the control group at both 4 and 12 weeks after the intervention ($p < 0.05$). These findings suggest that multicomponent exercise nursing interventions can effectively reduce frailty and improve activities of daily living and quality of life in elderly stroke patients with frailty.

KEYWORDS

elderly, stroke, frailty, multicomponent exercise, nursing intervention, activities of daily living, quality of life

1 Introduction

Frailty is characterized by a decline in physical function and increased vulnerability to imbalances after a stressful event (1). Frail individuals require comprehensive healthcare interventions, as they are at a higher risk for negative health outcomes like dependency and disability (2). This is especially common among older adults, who are more likely to experience accelerated decline in physical and cognitive abilities and have higher mortality rates (3). A systematic review and meta-analysis encompassing 1,187,000 individuals with stroke in 2022 revealed a frailty prevalence of 39.7% (4). Frailty can lead to a decline in motor function among patients (5). This deterioration in motor function can directly impair their ability to perform activities of daily living and subsequently affect their overall quality of life. Evidence indicates that the quality of life for patients experiencing frailty post-stroke is markedly lower compared to those without frailty, with a more pronounced decline observed over time (6). Frail stroke

individuals also have a higher risk of short and long-term mortality. Research has shown that frailty is a significant predictor of increased mortality within 3 months after a stroke (7). In addition, the patient's ability to perform activities of daily living is also an important issue for individuals with stroke. A systematic review demonstrated a robust correlation between stroke and activities of daily living, providing substantial evidence that stroke significantly impairs daily functioning in elderly individuals (8). This impairment underscores the critical importance of restoring physical activity in individuals with stroke. Therefore, it is crucial to implement appropriate treatment strategies to mitigate frailty in elderly individuals with stroke, improve activities of daily living, and minimize its adverse effects on health outcomes.

Non-pharmacological interventions are strategies that do not involve medication and are used for preventing, managing, or treating diseases and health conditions. These interventions aim to improve patients' quality of life, enhance functional abilities, and alleviate symptoms (9). Research suggests that non-pharmacological interventions, particularly exercise interventions, are effective in addressing frailty in the elderly (10). Implementing exercise interventions has been shown to improve frailty status, enhance daily activities, reduce anxiety and depression levels, and alleviate other negative emotional states (11). The 2018 International Conference on Skeletal Muscle Reduction Disorder and Frail Research (ICSFR) recommended the use of progressive multicomponent exercise interventions for frail older adults to promote healthy aging (12).

A comprehensive exercise program called multicomponent exercise, which includes flexibility, balance, coordination, resistance, and aerobic training, has been proven to improve muscle strength, balance, flexibility, and walking speed. This leads to better health outcomes for patients (13). Multicomponent exercise interventions have demonstrated clinical significance in a variety of diseases. A 12-month intervention study conducted in a Spanish community showed that a progressive and personalized multicomponent exercise program effectively reduced falls, improved frailty, and decreased mortality rates among older adults (14). Another cohort study on older adults recovering from COVID-19 in intensive care found that multicomponent exercise interventions significantly improved frailty, balance, gait, and muscle strength in this population (15). Additionally, multicomponent exercise is highly applicable to the elderly population. A study targeting elderly individuals in the community has demonstrated that multicomponent exercise can significantly improve frailty status and activity levels in the elderly (16). Multiple studies have indicated that multicomponent exercise can notably enhance the quality of life for older adults (17–19). In addition, the effects of the exercise are long-lasting. A cohort study in elderly individuals with diabetes showed a significant effect of a multicomponent exercise intervention (20). This suggests that the exercise has a profound effect on the health of patients. These interventions come in various forms and are easy to learn and implement with minimal limitations. Multicomponent exercise is widely recognized as the most effective approach to addressing frailty globally (12).

Nursing theories play a crucial role in guiding interventions and helping healthcare providers deliver patient-centered care. These theories ensure consistency and replicability across different settings, leading to a reduction in unnecessary medical procedures and costs. This results in more efficient resource utilization, improved health outcomes, and enhanced patient satisfaction (21). The PRECEDE-PROCEED model, based on health belief theory, comprehensively analyzes and predicts individual health behaviors, facilitating the development of impactful health education and promotion initiatives. This model, proposed by psychologist Irwin M. Green in the 1950s, has gained significant recognition in the fields of public health and behavioral sciences (22). Watson's humanistic Care model, developed by John Paul Watson, a philosopher and psychologist from Fordham University, emphasizes the importance of human emotions, relationships, and compassionate understanding in ethical conduct and decision-making. In this model, caregivers are driven by a genuine concern for the well-being and needs of others, rather than solely by duty or obligation. This model has been widely used in nursing interventions and has yielded notable results (23).

Although multicomponent exercise has shown significant effects on enhancing frailty, there is currently limited research on older adults who have had a stroke. In addition, many existing interventions lack theoretical foundations and fail to incorporate important motivational factors and compassionate care. This study aimed to develop a multicomponent exercise nursing intervention for elderly stroke patients with frailty, integrating elements of the PRECEDE-PROCEED model and Watson's caring theory. A randomized controlled trial was conducted to examine how multicomponent exercise nursing interventions affect the state of frailty, daily activities, and quality of life in elderly stroke patients with frailty. The findings of this study aim to provide new insights in the field of rehabilitation for elderly individuals with stroke.

2 Materials and methods

2.1 Study design

This single-blind, randomized controlled trial was conducted over a period of 3 months. The study received approval from the Research Ethics Committee of the Affiliated Hospital of Jiangnan University (LS2023064) and was registered at www.chictr.org.cn. Written informed consent was obtained from all participants. After baseline measurements were taken, the participants were randomly assigned to either the intervention (IG) or control (CG) groups using a random number table.

2.2 Participants

A total of 125 elderly stroke patients with frailty were recruited from a tertiary hospital in Wuxi city (Figure 1). The inclusion criteria were as follows: (1) patients who met the diagnostic criteria for acute ischemic stroke and were confirmed by head CT or MRI; (2) first episode, stable, and in the convalescent stage; (3) age $\geq$ 60 years; (4) FRAIL score $\geq$ 3; (5) bilateral upper and lower limb muscle strength $\geq$4 on the Lovett scale, and able to safely complete the 6-min walk test without assistance; (6) no physical or occupational therapy; (7) patients or caregivers proficient in operating smartphones; and (8) subjects voluntarily participated in the study and signed the informed consent. The exclusion criteria were: (1) accompanied by disturbance of consciousness or mental illness; (2) severe aphasia or communication disorder; (3) severe heart, lung, liver, kidney diseases, or malignant tumors; and (4) legal blindness or severe visual impairment.

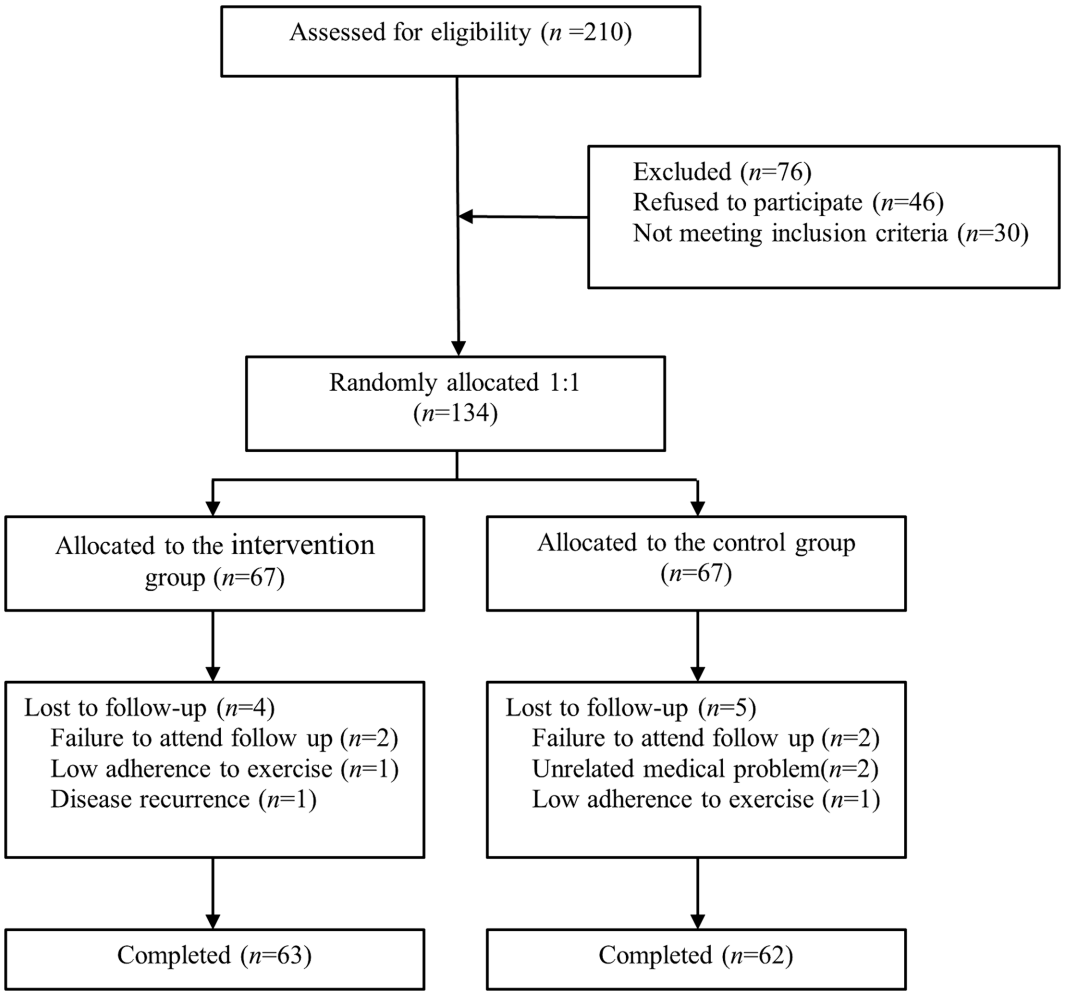

FIGURE 1
Flow chart of participants' enrollment.

2.3 Control group

The control group was administered standard neurological nursing care encompassing education on stroke-related conditions, medication effects, dietary and sleep recommendations, and the importance of exercise in stroke rehabilitation. Before discharge, patients received a comprehensive instructional video detailing exercise guidance. Post-discharge, patients participated in biweekly telephone follow-ups, during which nurses provided routine health education. This included highlighting the significance of smoking cessation, alcohol moderation, maintaining regular sleep patterns, and engaging in consistent physical activity for the prevention of recurrent strokes. Patients were also educated on self-monitoring techniques for essential physiological parameters such as blood pressure and blood glucose levels, and were encouraged to document their daily activity levels and dietary habits. Furthermore, strategies for emotional recognition and management were imparted to the patients.

2.4 Intervention group

A multicomponent exercise nursing intervention, developed through a literature review and Expert Panel Meeting, incorporated humanistic care, health education, and tailored exercise prescriptions. Grounded in Watson's Humanistic Care model, the program focused on patient and family needs, integrating care into daily treatment while monitoring psychological and emotional well-being. The protocol included trust-building and a comprehensive assessment of patients' psychological state, disease understanding, social support, routines, and exercise habits. Biweekly follow-up calls ensured adherence, addressed issues, and provided support. Health education, based on the PRECEDE-PROCEED model, aimed to modify behaviors and improve outcomes. On-site training guided patients and families in multicomponent exercises, with details on exercise suitability, frequency, and intensity. Post-discharge, regular follow-ups via outpatient services, phone consultations, and WeChat offered continued guidance and support (Table 1).

Seventy-two hours before discharge, patients and their families received instructions on a multicomponent exercise intervention, including specific movements, key safety points, and emergency protocols. A WeChat group was created to share exercise videos for review and practice. Family members were tasked with supervising the exercises and documenting attendance with photos at the start and end of each session. The study implemented a 12-week intervention cycle, and the program we implemented was as follows: week 1 to week 2—intervention once a week, week 3 to week 4—intervention twice a

TABLE 1 Multicomponent exercise prescription for elderly stroke patients with frailty.

Forms of exercise	Content of exercise	Phase 1	Phase 2	Phase 3	Phase 4
		1–2 weeks after discharge	3–4 weeks after discharge	5–8 weeks after discharge	9–12 weeks after discharge
Warm up	1. Neck exercise: gently spin the head in a clockwise direction and then counterclockwise direction. 2. Shoulder exercise: slowly rotate the shoulders in a back-and-forth and rotational movement. 3. Arm and wrist exercise: gently bend and straighten the arms while rotating the wrists. 4. Leg exercise: perform leg extension and rotational movements. 5. Ankle exercise: perform a gentle rotational motion of the ankles, moving them back and forth and from side to side.	5–10 min each time, RPE* 13–14	10–15 min each time, RPE 13–15	As before	As before
Aerobics	Walking or jogging	5–10 min each time, RPE 13 to 15	10–15 min each time, RPE 13–15	As before	As before
Daily living skills training	1. Walking and stair training. 2. Housework training: sweeping the floor, wiping the table, washing dishes, and other simple housework activities.	Walking and stair training, 5–10 min/time, housework training ≥1 item/day, RPE 13–15	Walking and stair training, 10–15 min/time, housework training ≥2 item/day, RPE 13–15	As before	As before
Elastic band resistance training	1. The elastic band is knotted and fixed at the height of the subject's ankle, the subject stands facing the elastic band and can maintain balance with the help of a support. 2. The subject stands on one leg and extends one leg backward, keeping the knee joint unbent for 15 s, alternating between the two legs.	5–10 min each time, RPE 13–15	10–15 min each time, RPE 13–15	As before	As before
Balance training	1. Sit with a Bobath handshake and try to stretch in all directions. 2. Gradually transition from double bridge to single bridge in supine position.	5–10 min each time, RPE 13–15	10–15 min each time, RPE 13–15	As before	As before
Flexibility training	Static stretching training: the patient was placed in the supine position and stretched the upper and lower limbs	5–10 min each time, RPE 13–14	10–15 min each time, RPE 13–15	As before	As before

*RPE: the Rating of Perceived Exertion.

week, week 5 to week 8—intervention five times a week, week 9 to week 12—intervention six times a week. Patient vital signs were monitored before and after the intervention, with biweekly follow-ups conducted either online or offline. Exercise intensity was evaluated based on the patients' subjective feelings during exercise, and the target intensity was determined using the Rating of Perceived Exertion (RPE). Based on our inclusion and exclusion criteria, we conducted preliminary experiments with six participants. The results indicated that the patients perceived the exercise intervention as causing a fatigue level of 13–15 on the 20-point RPE Borg scale (24). Therefore, we set the exercise intensity within this range to better match the exercise profile of this population. Patients were instructed to exercise within the target intensity range. We instructed patients to rest independently for mild discomfort and promptly alert researchers for symptoms such as paroxysmal chest tightness, palpitations, muscle weakness, headache, and other serious discomfort.

2.5 Outcomes measures

Data were collected at three time points: baseline, week 4, and week 12. This study employed a combination of on-site surveys and

online follow-up. Researchers were trained in standardized instruction language for surveying participants. The study objectives, training procedures, and key points were clearly communicated to the researchers. Individuals with stroke independently and anonymously completed questionnaires during on-site visits, which were then subjected to quality control by a designated officer. During the online follow-up intervention, follow-up nurses collected weekly data on the frequency and duration of patients' online logins. Previous studies have established that patients achieving a completion rate of 90% or higher were classified as having excellent adherence, while those with a completion rate below 90% were considered to have poor adherence.

The functional status of elderly stroke patients was assessed using the FRAIL scale, developed by the International Society for Nutrition and Aging. This scale consists of five components: fatigue, resistance, ambulation, illness, and weight loss. Scores on the scale range from 0 to 5, with higher scores indicating greater frailty. A score of 0 represents the absence of frailty, scores of 1–2 indicate pre-frailty, and scores of 3–5 indicate frailty. The Cronbach's α coefficient for this scale was calculated to be 0.826 (25).

The functional status of patients was evaluated using the Modified Barthel Index (MBI), which measures the ability to perform activities of daily living. The MBI consists of 10 components, and scores range from 0 to 100, with higher scores indicating higher proficiency. These scores are classified into four levels: 100 signifies no dysfunction, 61–99 indicates mild dysfunction, 41–60 indicates moderate dysfunction, and 0–40 indicates severe dysfunction. The internal consistency of the MBI, measured by the Cronbach's α coefficient, exceeded 0.92 (26).

The health status of elderly stroke patients was assessed using the Short Form Health Survey (SF-36), which includes 36 items measuring various dimensions of health. These dimensions include physical function (PF), role physical (RP), bodily pain (BP), general health (GH), mental health (MH), vitality (VT), social function (SF), and role emotional (RE). A conversion formula was applied to each dimension to calculate a total score ranging from 0 to 100, which serves as an indicator of the patients' quality of life. Higher scores indicate a better overall health status. The Cronbach's α coefficient of the scale ranged from 0.7 to 0.9 (27).

To evaluate the compliance of Multicomponent Exercise Nursing Intervention in Elderly Stroke Patients with Frailty, we investigated the compliance in the intervention group. Researchers conducted weekly telephone follow-ups to collect data on the frequency and duration of patients' exercise training sessions. Achieving 90% or more of the total prescribed exercise sessions during the intervention period was considered good compliance, while completing less was considered poor compliance.

2.6 Statistical analysis

Statistical analysis was performed using SPSS 22.0 software. Descriptive statistics were used to summarize measurement data, with normally distributed quantitative data presented as mean ± standard deviation and non-normally distributed data presented as median and interquartile range [M (P_{25}, P_{75})]. Counting data were presented as frequencies and percentages. Intergroup comparisons were performed using independent sample *t*-tests or non-parametric rank sum tests, while comparisons among different time points were conducted using repeated measures ANOVA or generalized estimating equations. The chi-square test was used to compare rates between groups. Two-sided *p* values less than 0.05 were considered statistically significant.

2.7 Sample size

The sample size for this study was determined using the formula $n_1 = n_2 = 2[(\mu_\alpha + \mu_\beta)\sigma/\delta]^2$, where pre-experiment data on frailty as the primary observation index indicated $\sigma = 3.71$ and $\delta = 2.64$. With significance levels $\alpha = 0.05$ and $\beta = 0.10$, the calculated sample size was $n_1 = n_2 = 42$ cases. To account for a 20% loss to follow-up, the final sample size was adjusted to 105 cases, which was ultimately increased to 125 cases in the actual study.

3 Results

A total of 125 elderly stroke patients were included in this study, with 63 cases in the intervention group and 62 cases in the control group. Table 2 shows that there was no statistically significant difference in the general information between the two groups ($p > 0.05$).

Frailty scores were compared between exercise and control groups at pre-intervention, 4 weeks, and 12 weeks post-intervention. The exercise group showed a significant reduction in scores over time (Pre: 3.37 ± 0.63; 4 weeks: 2.43 ± 0.56; 12 weeks: 1.66 ± 0.87), while the control group's scores remained stable (Pre: 3.33 ± 0.57; 4 weeks: 3.14 ± 0.43; 12 weeks: 3.15 ± 0.51). A repeated measures ANOVA showed significant effects of time and group on frailty scores, with a notable interaction indicating greater improvement in the exercise group ($F_{interaction} = 47.824$, $p < 0.001$, $\eta^2 = 0.388$). Significant differences were also found between groups ($F_{group} = 38.339$, $p < 0.001$, $\eta^2 = 0.512$) and over time ($F_{time} = 76.225$, $p < 0.001$, $\eta^2 = 0.505$). *Post-hoc* pairwise comparisons revealed significant reductions in frailty scores in the exercise group at both 4 and 12 weeks post-intervention ($p < 0.001$), with further improvement at 12 weeks compared to 4 weeks ($p < 0.05$). The control group showed no significant changes over the same periods (Table 3).

Table 4 shows the pairwise comparison of modified Barthel Scale scores over time for two groups. The exercise group ($n = 63$) had a significant score increase from pre-intervention [median (IQR): 85 (80, 85)] to 12 weeks post-intervention [90 (90, 95)], with improvements noted both compared to pre-intervention and 4 weeks post-intervention ($p < 0.05$). The control group ($n = 62$) showed no significant change from pre-intervention [82.5 (75, 90)] to 4 weeks [85 (80, 90)] and 12 weeks post-intervention [85 (80, 90)]. Statistical analysis showed notable differences between groups (Wald$\chi^2 = 34.397$, $p < 0.001$, $\eta^2 = 0.049$), over time (Wald$\chi^2 = 123.149$, $p < 0.001$, $\eta^2 = 0.607$), and in their interaction (Wald$\chi^2 = 42.380$, $p < 0.001$, $\eta^2 = 0.361$). *Post-hoc* tests revealed the exercise group scored significantly higher than the control group at 4 weeks ($z = -2.335$, $p = 0.021$) and 12 weeks ($z = -5.084$, $p < 0.001$) post-intervention.

The results of the repeated measures ANOVA for the SF-36 scores in each dimension are shown in Table 5. Significant within-group changes were observed for Physical Functioning (PF), Role Physical (RP), Bodily Pain (BP), General Health (GH), Vitality (VT), Social Functioning (SF), Role Emotional (RE), and Mental Health (MH)

TABLE 2 Comparison of general data between two groups ($n = 125$).

Variable	Intervention group ($n = 63$)	Control group ($n = 62$)	$t/\chi^2/Z$ value	p value
Age (years)	73.03 ± 7.53	73.50 ± 6.23	0.379 [a]	0.706
Gender (n, %)			0.008 [b]	0.927
Male	32 (50.8)	32 (51.6)		
Female	31 (49.2)	30 (48.4)		
Educational level (n, %)			5.708 [b]	0.127
Primary and below	26 (41.3)	17 (27.4)		
Junior high school	13 (20.6)	24 (38.7)		
High school	19 (30.2)	15 (24.2)		
College and above	5 (7.9)	6 (9.7)		
Medical insurance			0.656 [b]	0.418
Residents' medical insurance	47 (74.6)	50 (80.6)		
City and town medical insurance	16 (25.4)	12 (19.4)		
Monthly income			0.884 [b]	0.347
<3,000 yuan	43 (68.3)	47 (75.8)		
≥3,000 yuan	20 (31.7)	15 (24.2)		
Smoking (n, %)			0.068 [b]	0.794
No	49 (77.8)	47 (75.8)		
Yes	14 (22.2)	15 (24.2)		
Alcohol drinking (n, %)			0.670 [b]	0.413
No	56 (88.9)	52 (83.9)		
Yes	7 (11.1)	10 (16.1)		
Body mass index (BMI) (n, %)			3.640 [b]	0.162
<18.5 (underweight)	2 (3.2)	3 (4.8)		
18.5–23.9 (normal weight)	32 (50.8)	28 (45.2)		
≥24.0 (overweight or obese)	29 (46.0)	31 (50.0)		
Hypertension (n, %)			0.729 [b]	0.393
No	26 (41.3)	21 (33.9)		
Yes	37 (58.7)	41 (66.1)		
Diabetes mellitus (n, %)			1.993 [b]	0.158
No	47 (74.6)	39 (62.9)		
Yes	16 (25.4)	23 (37.1)		
Heart disease (n, %)			0.169 [b]	0.681
No	60 (95.2)	58 (93.5)		
Yes	3 (4.8)	4 (6.5)		
Degree of stroke			0.224 [b]	0.636
Normal	10 (15.9)	8 (12.9)		
Mildly	53 (84.1)	54 (87.1)		
Systolic blood pressure (mmHg)	143.38 ± 24.64	142.19 ± 14.13	−0.330 [a]	0.742
Diastolic blood pressure (mmHg)	74.75 ± 10.22	78.21 ± 12.03	1.736 [a]	0.085
Leucocyte (109/L)	5.94 ± 2.57	6.50 ± 1.31	1.533 [a]	0.129
Red blood cell (1,012/L)	4.31 ± 0.50	4.27 ± 0.47	−0.482 [a]	0.631
Blood platelet (109/L)	175.33 ± 48.29	188.84 ± 78.06	1.165 [a]	0.248
Hemoglobin (g/L)	127.35 ± 14.03	130.36 ± 14.76	1.167 [a]	0.246

(Continued)

TABLE 2 (Continued)

Variable	Intervention group ($n = 63$)	Control group ($n = 62$)	$t/\chi^2/Z$ value	p value
Fasting blood glucose (mmol/L)	5.66 ± 1.22	6.22 ± 2.31	1.665 [a]	0.099
Total cholesterol (mmol/L)	4.21 ± 0.99	3.94 ± 1.02	−1.488 [a]	0.139
Triglycerides (mmol/L)	1.33 (0.96,1.76)	1.47 (1.38,2.31)	0.588 [c]	0.558

[a]t value.
[b]χ^2 value.
[c]Z value.

TABLE 3 Pairwise comparison of Frail scale scores at different time points in the two groups (scores, $\bar{x} \pm s$).

Variable	n	Pre-intervention	4 weeks after intervention	12 weeks after intervention	F value	p value
Exercise group	63	3.37 ± 0.63	2.43 ± 0.56	1.66 ± 0.87	1.942	0.148
Control group	62	3.33 ± 0.57	3.14 ± 0.43[a]	3.15 ± 0.51[a,b]	98.104	<0.001***
t value		−0.350	7.882	11.629		
p value		0.727	<0.001***	<0.001***		

$F_{inter\text{-}group} = 38.339$, $p < 0.001$***, Eta-Squared (η^2) = 0.512; $F_{time} = 76.225$, $p < 0.001$***, $\eta^2 = 0.505$; $F_{interaction} = 47.824$, $p < 0.001$***, $\eta^2 = 0.388$.
[a]Compared with pre-intervention, $p < 0.05$*.
[b]Compared with 4 weeks after intervention, $p < 0.05$*.

TABLE 4 Pairwise comparison of modified Barthel scale score at different time points in the two groups [score, M (P_{25}, P_{75})].

Variable	n	Pre-intervention	4 weeks after intervention	12 weeks after intervention	F value	p value
Exercise group	63	85 (80,85)	85 (80,90)[a]	90 (90,95)[a,b]	121.548	<0.001***
Control group	62	82.5 (75,90)	85 (80,90)[a]	85 (80,90)[a]	7.970	0.001***
z value		−0.023	−2.335	−5.084		
p value		0.981	0.021*	<0.001***		

Wald$\chi^2_{inter\text{-}group} = 34.397$, $p < 0.001$***, $\eta^2 = 0.049$; Wald$\chi^2_{time} = 123.149$, $p < 0.001$***, $\eta^2 = 0.607$; Wald$\chi^2_{interaction} = 42.380$, $p < 0.001$***, $\eta^2 = 0.361$.
[a]Compared with pre-intervention, $p < 0.05$*.
[b]Compared with 4 weeks after intervention, $p < 0.05$*.

TABLE 5 Results of ANOVA of repeated measurement of SF-36 scores in each dimension before and after intervention in two groups.

Variable	Within-group			Inter-group			Interaction		
	F value	p value	η^2	F value	p value	η^2	F value	p value	η^2
PF	28.163	<0.001***	0.316	12.722	0.001***	0.094	29.884	<0.001***	0.329
RP	29.483	<0.001***	0.326	15.165	<0.001***	0.110	20.751	<0.001***	0.254
BP	17.487	<0.001***	0.223	0.265	0.608	0.002	5.995	0.001***	0.089
GH	125.490	<0.001***	0.673	62.253	<0.001***	0.336	118.760	<0.001***	0.661
VT	179.265	<0.001***	0.746	146.055	<0.001***	0.543	149.238	<0.001***	0.710
SF	191.262	<0.001***	0.758	8.092	<0.001***	0.062	41.227	<0.001***	0.403
RE	11.226	<0.001***	0.155	0.008	0.929	<0.001	2.165	0.119	0.034
MH	133.987	<0.001***	0.687	16.811	<0.001***	0.120	20.401	<0.001***	0.251

dimensions (all $p < 0.001$), indicating improvements over time within both groups. However, the BP dimension did not show a significant inter-group difference ($F = 0.265$, $p = 0.608$). Notably, the interaction effect was significant for all dimensions except Role Emotional (RE) and Bodily Pain (BP) ($p < 0.001$ for PF, RP, GH, VT, SF, MH; $p = 0.119$ for RE; $p = 0.001$ for BP), suggesting that the changes over time differed significantly between the exercise and control groups in most dimensions. Specifically, the interaction effect was strongest for Vitality (VT) ($F = 149.238$, $p < 0.001$) and Social Functioning (SF) ($F = 41.227$, $p < 0.001$). The inter-group comparison also revealed significant differences for Physical Functioning (PF) ($F = 12.722$, $p = 0.001$), Role Physical (RP) ($F = 15.165$, $p < 0.001$), General Health (GH) ($F = 62.253$, $p < 0.001$), Vitality (VT) ($F = 146.055$, $p < 0.001$), Social Functioning (SF) ($F = 8.092$, $p < 0.001$), and Mental Health

(MH) ($F = 16.811$, $p < 0.001$), while no significant difference was noted for Role Emotional (RE) ($F = 0.008$, $p = 0.929$).

The pairwise comparison of SF-36 scores in each dimension at different time points for both the exercise and control groups is presented in Table 6. Significant within-group improvements were observed in the exercise group for Physical Functioning (PF), Role Physical (RP), General Health (GH), Vitality (VT), Social Functioning (SF), and Mental Health (MH) dimensions over time

TABLE 6 Pairwise comparison of SF-36 scores in each dimension at different time points in the two groups (scores, $\bar{x} \pm s$).

Variable	Pre-intervention	4 weeks after intervention	12 weeks after intervention	*F* value	*p* value
PF					
Exercise group	40.63 ± 7.85	43.81 ± 10.03[a]	50.40 ± 12.19[a,b]	46.925	<0.001***
Control group	40.64 ± 8.94	37.26 ± 9.61[a]	39.19 ± 11.35	11.406	<0.001***
t value	0.007	−3.728	−5.315		
p value	0.995	<0.001***	<0.001***		
RP					
Exercise group	23.02 ± 6.81	33.33 ± 15.55[a]	41.67 ± 22.90[a,b]	48.772	<0.001***
Control group	24.60 ± 3.18	27.02 ± 6.86	25.81 ± 4.45	1.837	0.164
t value	1.667	−2.945	−5.396		
p value	0.100	0.004**	<0.001***		
BP					
Exercise group	89.49 ± 13.37	90.35 ± 10.23[a]	83.42 ± 7.83[a,b]	21.521	<0.001***
Control group	90.97 ± 11.98	90.15 ± 10.77	88.85 ± 10.93	2.117	0.125
t value	0.651	−0.104	2.047		
p value	0.516	0.917	0.043*		
GH					
Exercise group	30.95 ± 11.21	52.22 ± 7.22[a]	59.52 ± 8.17[a,b]	246.071	<0.001***
Control group	32.10 ± 13.04	32.74 ± 13.23	32.58 ± 15.88	0.146	0.865
t value	0.526	−10.191	−11.899		
p value	0.600	<0.001***	<0.001***		
VT					
Exercise group	25.48 ± 6.58	41.75 ± 11.68[a]	59.60 ± 11.26[a,b]	330.317	<0.001***
Control group	25.32 ± 7.83	25.48 ± 9.04	26.94 ± 10.65	0.822	0.442
t value	−0.119	−8.713	−16.657		
p value	0.906	<0.001***	<0.001***		
SF					
Exercise group	38.80 ± 14.92	59.96 ± 10.28[a]	76.37 ± 9.67[a,b]	205.958	<0.001***
Control group	44.98 ± 21.63	51.08 ± 17.59[a]	58.06 ± 17.24[a,b]	27.955	<0.001***
t value	1.858	−3.442	−7.304		
p value	0.066	0.001***	<0.001***		
RE					
Exercise group	37.57 ± 11.19	42.33 ± 14.91[a]	47.09 ± 18.58[a,b]	11.688	<0.001***
Control group	40.32 ± 13.68	41.94 ± 14.70	44.09 ± 17.88	1.783	0.173
t value	1.232	−0.148	−0.921		
p value	0.220	0.882	0.359		
MH					
Exercise group	40.89 ± 9.21	45.21 ± 10.67[a]	54.54 ± 10.69[a,b]	128.637	<0.001***
Control group	38.93 ± 9.71	41.10 ± 7.50[a]	44.77 ± 7.02[a,b]	26.568	<0.001***
t value	−1.164	−2.494	−6.048		
p value	0.062	0.014*	<0.001***		

[a]Compared with pre-intervention, $p < 0.05$*.
[b]Compared with 4 weeks after intervention, $p < 0.05$*.

(all $p < 0.001$). For example, the PF score increased from a mean ± SD of 40.63 ± 7.85 at pre-intervention to 50.40 ± 12.19 at 12 weeks post-intervention. Similarly, the GH score improved significantly from 30.95 ± 11.21 to 59.52 ± 8.17 over the same period. In contrast, the control group showed no significant within-group changes in PF, RP, VT, SF, or MH dimensions ($p > 0.05$), although there was a slight improvement in GH scores which was not statistically significant ($p = 0.865$). The Role Emotional (RE) dimension did not exhibit significant changes over time in either group ($p > 0.05$). Significant inter-group differences were found for PF, RP, GH, VT, SF, and MH dimensions at 12 weeks post-intervention (all $p < 0.001$), indicating that the exercise group experienced greater improvements compared to the control group. For instance, the VT score in the exercise group increased from 25.48 ± 6.58 to 59.60 ± 11.26, whereas it only marginally increased from 25.32 ± 7.83 to 26.94 ± 10.65 in the control group. No significant inter-group differences were noted for RE ($p > 0.05$). The interaction effect was significant for PF, RP, GH, VT, SF, and MH (all $p < 0.001$), highlighting that the changes over time were more pronounced in the exercise group compared to the control group. However, the interaction for RE was not significant ($p = 0.119$).

Following a 4-week intervention, 51 individuals (80.9%) in the intervention group demonstrated satisfactory compliance. This number decreased to 48 individuals (76.2%) with satisfactory compliance after a 12-week intervention period. No falls, muscle injuries, or joint problems were reported in the intervention group throughout the intervention duration.

4 Discussion

To the best of our knowledge, this study is the first randomized controlled trial to implement a multicomponent exercise nursing model in elderly stroke patients with frailty. The trial compares the effects of a multicomponent exercise nursing model with a standard nursing approach on frail elderly stroke patients, focusing on factors such as frailty, activities of daily living, and quality of life. The findings indicate that the multicomponent exercise nursing intervention is effective in improving the frailty status of elderly stroke patients. Furthermore, significant improvements were observed in both functional capacity for activities of daily living and overall quality of life.

Stroke patients are at an increased risk of developing frailty due to advanced age and the sudden onset of the disease. Frailty, in turn, serves as an independent risk factor for cardiovascular and cerebrovascular diseases, creating a cyclical relationship. Research shows that stroke patients with frailty experience a lower health-related quality of life and a more pronounced decline in health compared to non-frail patients (6). Consistent with the findings of this study, multicomponent exercise has been shown to be effective in improving frailty in older patients hospitalized for heart failure (28). Multicomponent exercise, which combines various exercises, has been shown to enhance cardiopulmonary function, increase muscle strength, flexibility, and coordination, reduce the risk of falls, and promote mental well-being. Its benefits extend to conditions such as Alzheimer's disease (29, 30), breast cancer (31), hypertension (32), and diabetes (20). The endorsement of multicomponent exercise by the World Health Organization (WHO) as a tool for developing personalized exercise regimens underscores its effectiveness and importance (33).

Individuals with stroke are at risk of experiencing a decline in activities of daily living, which can have long-term consequences if not addressed promptly. For elderly individuals, participating in comprehensive exercise programs is crucial for restoring independence in daily life activities. Achieving independence not only reduces the burden on caregivers but also enhances overall well-being. A randomized controlled trial conducted among frail elderly individuals in the community demonstrated that participation in a multicomponent exercise regimen effectively improves ADL (34), which aligns with the findings of the present study. Frailty has been shown to lead to decreased endurance, muscle strength, balance function, gait, and body flexibility in patients. Multicomponent exercise training combines the features and benefits of different training methods, thereby enhancing overall body function in frail patients and ultimately improving their frailty status (35).

The multidimensional concept of quality of life includes aspects such as physical health, psychological well-being, social connections, and environmental satisfaction. This research illustrates that a multicomponent exercise nursing intervention can enhance patients' quality of life, which aligns with findings from previous studies (36). Physical exercise has the potential to improve physical health, facilitate functional recovery, stimulate the release of endorphins (37), alleviate anxiety and depression (38), and enhance self-esteem and self-assurance among patients. Physical exercise has also been shown to improve social interactions and foster a sense of belonging and participation within a community (39). Moreover, Watson's humanistic care theory emphasizes the importance of addressing individual patient needs and values, as well as monitoring psychological and emotional well-being. By incorporating the principles of humanistic care into a multicomponent exercise nursing intervention, the overall quality of life for patients can be significantly enhanced.

The high adherence observed in our study is consistent with findings from a previous multicenter randomized controlled trial (40). This may be attributed to the integration of the PRECEDE-PROCEED model and humanistic care model in our study, as well as the utilization of nursing theory to enhance patient motivation (41). The incorporation of the PRECEDE-PROCEED model has been shown to effectively guide the planning, implementation, and evaluation of health promotion programs. This model provides a systematic framework for planning and evaluating health behavior change interventions through the use of flowcharts (22). Unlike traditional approaches where patients passively receive education from nurses, this model emphasizes empowering patients to take an active role in their own healthcare decisions, promoting sustained compliance and improved health outcomes. Numerous studies have demonstrated the successful application of this theory to diseases such as diabetes (42, 43), hypertension (44, 45), and obesity (46, 47). Watson's humanistic care theory emphasizes the significance of humanistic care and the importance of showing respect for individuals within the nursing profession. At the core of Watson's theory is the idea that nursing is a moral and philosophical endeavor aimed at enhancing the well-being of individuals, families, and communities (23). Nurses are responsible for assisting patients in achieving physical, mental, emotional, and spiritual equilibrium through compassionate interactions (48). The application of this theory to primipara (49), dementia patients (50),

and end-stage patients (51) has been shown to enhance patient quality of life and satisfaction. This study integrates these two nursing theories into the intervention program, resulting in improved patient compliance and enhanced implementation effectiveness.

Throughout the course of this study, no adverse events such as falls or muscle and joint injuries occurred, indicating the program's strong emphasis on safety and scientific rigor. The program framework was developed based on expert consensus, guidelines, and the specific physical and psychological needs of elderly stroke patients, utilizing the PRECEDE-PROCEED model (52) and humanistic care model. The exercise content was tailored to better suit the frailty of elderly stroke patients. After the initial draft, a meeting was held with a panel of experts from various clinical specialties, including neurology, clinical nursing, stroke rehabilitation, nursing management, and psychotherapy, all with extensive clinical experience. Based on feedback from preliminary experimental results, adjustments were made to the intensity and content of the intervention, following the principles of gradual and individualized intervention measures. The finalized version of the intervention program for elderly individuals with stroke was formulated. Therefore, the intervention program of this study is scientifically sound to some extent.

This study has certain limitations. Firstly, the randomized controlled trial had a duration of only 3 months, requiring further long-term follow-up to assess the intervention's lasting effects. Secondly, the patient sample was limited to a Class iii Grade A hospital in Wuxi City, potentially limiting its generalizability. Future research should involve multi-center, large-sample trials to confirm the feasibility and effectiveness of the intervention. In addition, the control group in this study received standard care instead of a targeted exercise intervention. It is recommended that future research compare the multicomponent exercise intervention with a specific exercise intervention to further validate the effectiveness of the former. Furthermore, to ensure the safety of the trial, this study exclusively included patients with a muscle strength of at least grade 4. This criterion inherently limited the generalizability of the study's findings. Additionally, the study did not account for the lesion location or the affected hemisphere, factors which could potentially influence the outcomes. Future research should aim to broaden the inclusion criteria and conduct a more nuanced analysis of patients with varying conditions to enhance the generalizability and accuracy of the results.

5 Conclusion

The findings of the present study suggest that among elderly stroke patients with frailty, a multicomponent exercise nursing intervention is safe, feasible, and has the potential to significantly improve patients' frailty status, activities of daily living, and quality of life compared to routine nursing care. Future research should consider including additional evaluation measures to provide a more comprehensive assessment of the impact of a multicomponent exercise nursing intervention in this population.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Research Ethics Committee of the Affiliated Hospital of Jiangnan University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

YL: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Writing – original draft. JH: Conceptualization, Data curation, Formal analysis, Investigation, Software, Validation, Writing – original draft. LZ: Methodology, Writing – review & editing. YH: Validation, Writing – review & editing. ZL: Data curation, Validation, Writing – review & editing. YC: Funding acquisition, Visualization, Writing – review & editing. YQ: Resources, Supervision, Writing – review & editing. ZS: Funding acquisition, Project administration, Resources, Writing – review & editing. RS: Funding acquisition, Project administration, Supervision, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Osteoporosis: a problem still faulty addressed by the Romanian healthcare system. Results of a questionnaire survey of people aged 40 years and over

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Purpose: We aimed to investigate the knowledge and awareness level of osteoporosis, its risk factors, the possible causes of underdiagnosis, as well as the preventive measures and lifestyle behavior of the Romanian population.

Patients and methods: A non-interventional, cross-sectional study was performed, consisting of an in-person survey, in 10 pharmacies located in both urban and rural settings in Romania. The survey was distributed to patients ≥40 years old.

Results: Of 189 respondents, 78.8% were women, the majority age group being 60–69 (31.7%) and 50–59 (30.7%) years old and coming from urban areas (69.3%). Although 75.1% of participants declared knowing about osteoporosis, having a moderate level of knowledge, and women being more aware of the pathology, 77.3% have never performed a DXA test. Moreover, participants already diagnosed with osteoporosis did not show a better disease knowledge than those without a diagnosis. Nearly half of the respondents did not know that a family history of the disease increases the risk of developing it and 60% of them thought that symptoms may develop before a fracture occurs. The preventive strategies tend to be disregarded and thus, underused. Moreover, 42.9% of participants reported being diagnosed with osteoporosis, do not undergo treatment, although they are aware of the existence of effective strategies. The dataset was used to build a participant compatibility network. The network's clustering revealed six relevant communities, which are not correlated with questionnaire results but reflect the patterns of feature associations.

Conclusion: Preventive and therapeutic osteoporosis education programs are urgently needed in the Romanian population to decrease disability and high mortality risks and thus, to improve the quality of life.

KEYWORDS

antiresorptive medication, underdiagnosed, knowledge, awareness, prevention, Romanian primary care

1 Introduction

Osteoporosis is a systemic skeletal disease that affects the balance between bone formation and bone resorption, leading to an altered bone density and microarchitecture, and, consequently, increasing the likelihood of fragility fractures. Depending on the underlying causes, osteoporosis is classified as primary or secondary (1–8).

Postmenopausal osteoporosis and age-related or senile osteoporosis are the two types of primary osteoporosis, affecting both women and men (1, 2, 9). Senile osteoporosis may occur in any older adult over the age of 70. It is rooted in some of the aging processes, such as increased parathyroid hormone levels, low-grade inflammatory processes, osteoblast dysfunction, low calcium levels and vitamin D deficiency (2). In the elderly population, bone loss accelerates with increasing age (10, 11). In contrast to postmenopausal osteoporosis, senile osteoporosis associates higher rates of low-bone turnover, increased and, decreased bone formation (12).

Secondary osteoporosis has multiple causes, including endocrine and metabolic disorders, certain diseases, and a number of medicines (1, 2, 4, 9) (i.e., glucocorticoids, proton pump inhibitors, antiepileptics, heparin, lithium, chemotherapy and immunosuppressants, thiazolidinediones, aromatase inhibitors, parenteral nutrition, sodium-glucose cotransporter-2 inhibitors, supraphysiologic doses of thyroid hormones, and selective serotonin reuptake inhibitors used as a long-term treatment or in a high dose regimen) (4, 13).

In recent years, the prevalence of osteoporosis has increased, thereby escalating the economic burden of the disease (4, 14). 18.3% of the world's population is affected by osteoporosis, women having a higher risk of developing the condition compared to men (9). In Romania, the prevalence of osteoporosis is lower than the European average, with 4.8% of Romanian patients aged 50 years or older being diagnosed with the disease, compared with 5.6%, EU's average (15). Osteoporotic fractures often lead to pain and disability, and more than 50% of the patients with a hip fracture are unable to regain independently living (2, 4, 13, 15).

One of the most important tools in managing osteoporosis is the assessment bone mineral density (BMD), typically performed using dual-energy X-ray absorptiometry (DXA) scanning. The assessment identifies the patient's risk level, detects the presence of osteopenia or osteoporosis, guides clinicians to select appropriate medication, and aids in monitoring the disease and effectiveness of treatment. It is estimated that at least 11 DXA machines per million people are required for adequate assessment of osteoporosis and for monitoring patients undergoing treatment. Yet, due to insufficient equipment, Romania falls into the category of European countries lacking proper DXA machines, which may be a cause of the underdiagnosis of osteoporosis (15).

A wide range of drugs have been approved and are available for the prevention and treatment of osteoporosis: bisphosphonates, RANK—ligand inhibitor, selective estrogen receptor modulators, parathyroid hormone analogs, and sclerostin inhibitor (13). However, in Romania, a significant percentage of individuals at high risk of fractures do not receive treatment, the treatment gap among osteoporotic women being 78% in 2019 (15). Despite the existence of clinical guidelines, some patients remain undiagnosed even after experiencing a fracture (13, 15, 16). Moreover, in a previously published STOPP/START v.2 criteria-based study, our research group reported a lack of prescription of antiresorptive or anabolic bone therapy for documented osteoporosis in patients from rural and urban areas of Romania (17, 18).

The aging population (expected to rise to 29% by 2050, compared to 19.7% in 2018 in EU) is the main catalyst for the onset of frailty syndrome, characterised by increased vulnerability due to physical, mental, and social decline (19). Elderly people with poor diet, sedentary lifestyle, and comorbidities such as cardiovascular diseases, osteoporosis, dementia, diabetes mellitus, and cancer are at high risks of developing frailty (20, 21). Features of frailty include limited mobility, susceptibility to falls and fractures, frequent and prolonged hospitalizations, and increased mortality rates (22).

In Romania, CVDs are the leading cause of death, accounting for 59.3% of all deaths nationwide (23). Romania also ranks second in Europe in terms of the proportion of elderly individuals with disabilities, with a large number of people reporting walking difficulties. Hence, effective approaches in the prevention and treatment of osteoporosis in a high cardiovascular risk population will decrease the risk of frailty among elderly Romanians.

Given the aforementioned challenges, we aimed to investigate the level of knowledge and awareness of osteoporosis and associated risk factors among the Romanian population. Our objective was to identify the possible causes of underdiagnosis of osteoporosis via an in-person survey. In addition, since osteoporosis is preventable, we also sought to observe preventive measures and lifestyle behaviors of the study participants. To our knowledge, this is the first Romanian study that intends to evaluate the population's understanding of osteoporosis and its risk factors. Our work can serve as a starting point for further research and an alarm signal for the general public to better comprehend and manage this pathology, in order to decrease frailty.

2 Materials and methods

2.1 Study design

A non-interventional, cross-sectional study was conducted over 3 months (from February 1, 2023, to April 30, 2023) in 10 pharmacies located in both urban and rural areas across four Romanian counties: Timiș, Arad, Caraș-Severin, and Olt. The study was designed around a self-administered questionnaire, distributed to patients who visited the community pharmacies included in the research. A total of 189 participants were selected for the study. Written informed consent was obtained from all the respondents.

Abbreviations: BMD, Bone mineral density; BMI, Body mass index; CVDs, Cardiovascular diseases; DXA, Dual-energy X-ray absorptiometry; GP, General practitioner; ICC, Intraclass coefficient; PPI, Proton pump inhibitors.

2.1.1 Inclusion and exclusion criteria

The survey included participants of 40 years old or above, able to read and write in Romanian and willing to fill in the questionnaire. Respondents below 40 years old, those with language barriers or with signs of cognitive impairment, and those unwilling to participate in the study were not included. We also excluded any questionnaires that were incompletely answered.

2.1.2 Sampling methodology of the pharmacies included in the study

First, a representative sample of pharmacies from different areas was established to reflect a balanced urban-rural distribution and the socio-economic diversity of patients. The targeted pharmacies were selected based on predetermined criteria [urban areas: both from in the municipality cities, centrally located, with a high flow of clients/patients from all over the county, recognized as well-stocked, and from smaller towns located at least 50 km from the municipality; rural areas: pharmacies in villages closer to a larger town (about 20 km) and at a greater distance from the town (minimum 30 km)], without subjective intervention by the researchers. Next, the selection of pharmacies was randomized from a complete list of available pharmaceutical establishments in the study region using a randomization algorithm. This process ensured that no pharmacy was included or excluded based on its specific characteristics.

A total of 26 pharmacies were contacted. Ten pharmacies agreed to collaborate and were included in the study, each pharmacy receiving 60 printed questionnaires (600 distributed questionnaires). At the end of the study period, although 375 questionnaires were returned, only 189 questionnaires were fully completed and were included in the study.

2.2 Data collection and research tool

A number of pharmacies were invited and agreed to collaborate in the research. Each pharmacy delegated two pharmacists to handle data collection, with the responsibility of informing the participants about the study specifics, providing the questionnaire, and ensuring any participant questions were clarified. After ensuring the participants of complete confidentiality and anonymity of their responses, the written informed consent was obtained. Two designated persons entered the data into a Microsoft Excel Sheet, with each questionnaire assigned a unique identification number to allow for error checking for each respondent. A third person then randomly reviewed the input data to confirm its accuracy. Lastly, the body mass index (BMI—kg/m^2) was calculated based on the height and weight provided by the participants. Thus, a BMI value <18.5 kg/m^2 is characteristic of underweight people, a BMI between 18.5 and 24.9 kg/m^2 is considered as normal weight, overweight is represented by a BMI 25–29.9 kg/m^2 and obesity is considered as >30 kg/m^2 (24, 25). The questionnaire was developed based on the European, Canadian and French sources available in the specialty literature (26–30). The final version of questionnaire consisted of 31 items, including both dichotomous and multiple answers questions, and was subsequently pre-tested and validated. The survey began by describing the study's objective and assuring participants of the confidentiality and anonymity of their responses.

The first part of the questionnaire (questions 1–7) intended to collect socio-demographical data, including age, sex, height, weight, education level, residency, and the residency of their general practitioner (GP). The following section (questions 8–9) evaluated the respondents' sources of information about osteoporosis (e.g., physician, social networks, family, friends), if applicable.

Next part of the questionnaire (question number 10) concerned 13 items that set out to assess the level of knowledge regarding osteoporosis and its risk factors using "yes or no" responses. Each correct answer was assigned 1 point, while incorrect answers received 0 points, resulting in a maximum score of 13 points. Participants' knowledge scores were then categorized into three different levels: those scoring 50% or less (fewer than 7 points) were categorized as having low knowledge, those scoring between 50 and 75% (7–10 points) were categorized as having moderate knowledge, and those scoring over 75% (11 points and more) were categorized as having high knowledge.

The middle part of the survey (questions 11–26) collected information on personal medical history, heredo-collateral history, and use of certain medications for more than 3 months. Additionally, it included questions about nutrition and lifestyle, such as calcium and vitamin D intake, daily physical exercise, smoking, alcohol intake, and caffeine consumption habits.

Lastly, the questionnaire (questions 27–31) identified the participants who are at risk of have developed osteoporosis. For those already diagnosed, we gathered data on the administered treatment and we evaluated to which extent the DXA test was performed as a preventive or diagnostic measure.

2.3 Validation and reliability

The validity of the survey was determined by a three-stage assessment process with a committee of specialists.

2.3.1 Pre-validation stage

The first version of the questionnaire was drafted by a group of professionals: a general practitioner, a clinical pharmacist, a clinical pharmacy resident and a pharmacy student. A second group of specialists (an endocrinologist, an orthopedist and a public health physician) ensured that the questionnaire is clinically appropriate.

2.3.2 Constructive validation phase

The questionnaire was distributed to a small group of participants ($n = 10$) to solicit input on the questions' clarity, understanding, and relevance. The suggestions were documented and used to revise and improve the questionnaire.

2.3.3 Empirical validation phase

To assess its psychometric properties, the questionnaires were distributed in 2 rural pharmacies and 2 urban pharmacies (8 questionnaires per pharmacy). Internal consistency and test-retest reliability were determined. Test-retest reliability was calculated through intraclass coefficient (ICC), and the results showed an ICC value of 0.65 and an alpha coefficient of 0.6. This reflects moderate

internal consistency and indicates the items are largely homogeneous, supporting the validity of the present questionnaire.

2.3.4 Ethical considerations

This study was conducted in accordance with the Declaration of Helsinki and its latest amendments. Furthermore, it was approved by the Ethics Committee of the "Victor Babes" University of Medicine and Pharmacy (no.47/2024). As aforementioned, written informed consent was also obtained from all respondents.

2.4 Statistical analysis

The statistical analysis was performed using Statistical Package for Social Science Version 22 (IBM, Armonk, NY, United States) at a statistical significance level of 0.05 ($p < 0.05$). Kolmogorov–Smirnov test was used to assess data normality. All categorical variables were expressed as number and percentage, whereas quantitative data were represented as mean and standard deviation. The Student t-test, ANOVA test, chi-square test and Spearman's correlation test were used to compare and identify the associations between the knowledge score and the studied variables.

2.5 Complex network-based analysis

The network analysis of the osteoporosis dataset assumes the building of a graph $G = (V, E)$, where the vertices v_i (from the vertex set V, $v_i \in V$) represent the participating individuals, and the undirected edges e_{ij} between vertices v_i and v_j represent a compatibility relationship between individuals i and j. We then apply network clustering on G, using the energy layout in Mathematica 11.1.1 to generate participant communities (or clusters).

Figure 1 presents the clustered network G, where node colors depict the corresponding participant's level of knowledge according to the questionnaire results. We define compatibility between two participants based on the individual features recorded in the osteoporosis dataset. These features are classified into 4 classes: anthropometric, demographic, lifestyle, and clinic. Accordingly, two participants i and j are compatible (i.e., we have an edge e_{ij} between v_i and v_j) if they are compatible according to at least 3 out of 4

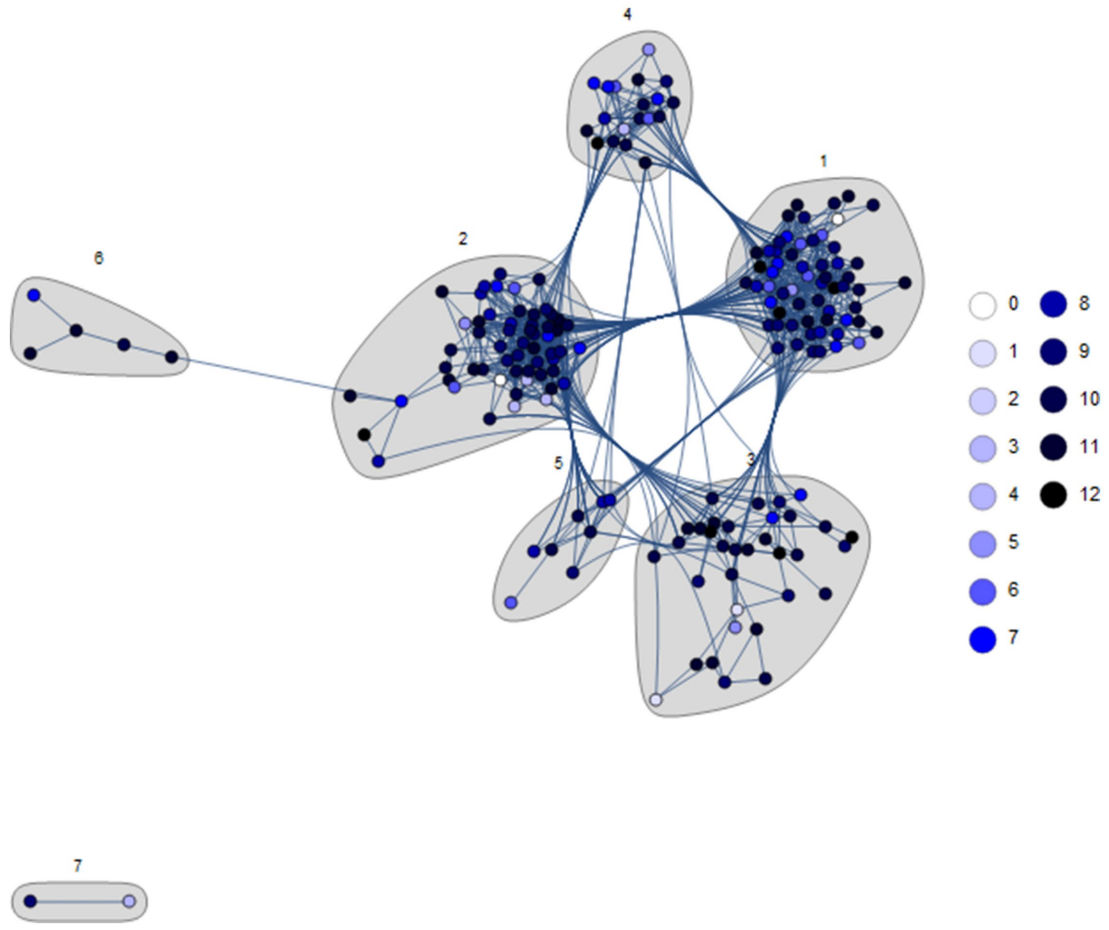

FIGURE 1
The participants' network G was built according to participant compatibility relationships and clustered with the energy layout; the node colors represent the participants' questionnaire results. The number of participants in the dataset is 189; however, 4 vertices have no edge, so the number of vertices in G is $|V| = 185$. The clustering reveals 7 distinct participant communities, emphasized with a gray background. The first 6 communities pertain to the main connected component, while Community 7 is disconnected.

compatibility classes. The anthropometric class comprises the following features: age, sex, and body mass index (BMI). The age is an integer number, but we discretize it by defining 5 age intervals: 40–49, 50–59, 60–69, 70–79, and 80–89. We use 4 discrete BMI levels: <18.5 (underweight), 18.5–24.9 (normal weight), 25.0–29.9 (overweight), and ≥30 (obesity). The demographic class features are the education level (low and high) and living environment (rural and urban). The following characteristics are binary in our analysis: calcium supplements, vitamin D supplements, alcohol, coffee, smoking, physical activity, fracture history, comorbidities, osteoporosis diagnosis, DXA scan, and osteoporosis treatment. We assign the participant compatibility according to the feature class as follows: for the anthropometric class, 2 out of 3 identical features; for the demographic class, 2 out of 2; for the lifestyle class, 5 out of 6; and for the clinic class, 4 out of 5. Our analysis of the cluster structure in Figure 1 excludes the 4 vertices (i.e., participants) without edges, as well as 2 vertices in community/cluster 7 (disconnected from the main connected component). Therefore, our investigation includes the 183 vertices in communities 1–6 from Figure 1. The edge density distribution in network G determines the segregation of communities, while the feature compatibility defines the presence of edges. Consequently, the association of features is linked to the community characterization. Indeed, although many possible combinations exist for the 16 features considered, the main component reveals only 6 communities that exhibit specific feature associations.

3 Results

Of the 600 questionnaires initially distributed, 375 were returned, but only 189 were fully completed, and thus, they were included in the present study.

The socio-demographic data of our survey group are systematically presented in Table 1. Women were overrepresented, accounting for 78.8% ($n = 149$) of the 189 respondents, while men made up 21.2% ($n = 40$). The majority of respondents were distributed across the age groups of 50–59 (30.7%, $n = 58$) and 60–69 (31.7%, $n = 60$), indicating a higher representation of middle-aged and senior individuals, while other age groups were less well represented, with 21.2% participants ($n = 40$) of 40–49 group, 14.0% participants ($n = 27$) of 70–79 group and 2.1% participants ($n = 4$) of 80–89 group. The overall mean age was 58.9 years with a standard deviation of 10.24 and the median age was 59 years old, with a range between 40 and 85 years. A larger proportion of participants came from urban areas (69.3%), while the remainder lived in rural areas (30.7%). In terms of education level, the largest share is represented by respondents with high school education (40.2%), followed by those with higher education (34.9%).

TABLE 1 The absolute (count) and relative (%) frequency of socio-demographic characteristics.

Variable	Value	Count (n=)	%
Gender	Male	40	21.2%
	Female	149	78.8%
Age range	40–49	40	21.2%
	50–59	58	30.7%
	60–69	60	31.7%
	70–79	27	14.3%
	80–89	4	2.1%
Residency	Rural	58	30.7%
	Urban	131	69.3%
Level of education	Secondary school	25	13.2%
	High-school	76	40.2%
	Post-secondary school	22	11.6%
	University	66	34.9%

Table 2 presents the frequency of responses regarding osteoporosis signs, symptoms, risk factors, family history, prevention, diagnosis, management, and treatment. Although most participants (75.1%) reported having knowledge about osteoporosis, a little more than one-quarter received information about the disease from a physician (26.2%). Instead, social media was the main source of information (27.7%). Moreover, less than a half (39.2%) of respondents had been informed by their general practitioner about the risk of developing osteoporosis.

Based on the 13 questions in Table 3 and the knowledge cut-off points presented in the methods section, we assessed the participants' level of knowledge on osteoporosis. Out of the total number of 189 subjects, 126 subjects (66.7%) were identified as having moderate knowledge, 40 (21.2%) as having high knowledge, and 23 (12.2%) as having low knowledge. The overall mean and standard deviation of total knowledge was 9.02 ± 0.15. Individual assessment of responses helped identify the less known information about this pathology among the studied population. Most participants were aware that osteoporosis benefits from effective treatments (98.4%), increases the risk of fractures (94.2%), and is more common in females (91.5%). Conversely, 46.0% of respondents were unaware that a family history of osteoporosis predisposes to the disease. More than half of participants incorrectly believed that osteoporosis causes symptoms before fractures occur (59.3%) and that a fall is not a factor as important as low bone density in the development of fractures (64.0%). Moreover, 72.5% of the responses to the question whether any type of physical activity is suitable for osteoporosis were erroneous.

We also evaluated the effect of some of the studied variables on the score of osteoporosis knowledge level (Table 4). Women showed a significantly higher level of knowledge about osteoporosis compared to men ($p = 0.008$). Patients with a family history of osteoporosis also scored a significant higher score compared to those without a family history, with an average score of 9.6 versus 8.8 correct responses, respectively ($p = 0.05$). The participants' level of knowledge about osteoporosis was unaffected by age, residence, education level, recent falls, osteoporosis diagnosis, BMI and sources of information. Additionally, a positive correlation (rho = 0.153, $p = 0.036$) was observed between knowledge level score and duration of daily physical activity, suggesting that respondents that know more about osteoporosis engage in more daily physical activity.

Next points in the survey evaluated participants' risk of developing osteoporosis and potential prevention practices (Table 2). A significant proportion of subjects were overweight (44.5%) or obese (27.0%), with an overall average BMI of 27.6 ± 4.55. About a quarter (24.3%) of respondents have suffered a recent fall, with falls from a standing height (14.8%) being the most prevalent, being thus predisposed to fractures. Family history of osteoporosis was recorded in 16.9% of

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TABLE 2 The absolute (count) and relative (%) frequency of responses corresponding to osteoporosis signs, symptoms, risk factors, family history, prevention, diagnosis, management and treatment.

Variable	Value	Count (*n*=)	%
Knowledge about osteoporosis	No	47	24.9%
	Yes	142	75.1%
Source of information	Physician	50	26.2%
	Social networks	52	27.7%
	Family/friends	48	25.5%
	Others (radio/TV)	39	20.6%
BMI	Underweight (<18.5 kg/m^2)	3	1.6%
	Normal weight (18.5–24.9 kg/m^2)	51	27.0%
	Overweight (25–29.9 kg/m^2)	84	44.5%
	Obesity (>30 kg/m^2)	51	27.0%
Recent falls (in the last year)	No	143	75.7%
	Yes	46	24.3%
Bone fractures in the past	No	147	77.8%
	Yes	42	22.2%
Family history of fracture	No	157	83.1%
	Yes	32	16.9%
Taking calcium supplements	No	135	71.4%
	Yes	54	28.6%
Taking vitamin D supplements	No	116	61.4%
	Yes	73	38.6%
Alcohol consumption	No	129	68.3%
	Occasionally	9	4.8%
	Yes	51	27.0%
Caffeine consumption	No	44	23.3%
	Yes	145	76.7%
Active smoker	No	148	78.3%
	Yes	41	21.7%
Daily physical exercises	<30 min/day	86	45.5%
	30–60 min/day	58	30.7%
	>60 min/day	45	23.8%
Family history of osteoporosis	No	157	83.1%
	Yes	32	16.9%
Information on the risk of developing osteoporosis from general practitioner	No	115	60.8%
	Yes	74	39.2%
Osteoporosis diagnosis	No	161	85.2%
	Yes	28	14.8%
DXA bone quality test	No	146	77.3%
	Yes	43	22.8%
Osteoporosis treatment	No	12	42.9%
	Yes	16	57.1%
Type of treatment	Bisphosphonates	10	62.5%
	Denosumab	2	12.5%
	Teriparatide	4	25.0%

TABLE 3 Evaluation of individual responses to the osteoporosis knowledge level assessment.

Statement	Statement validity	Number (%) of correct answers	Number (%) of incorrect answers
1. A family history of osteoporosis strongly predisposes a person to this disease	True	$n = 102$ (54.0%)	$n = 87$ (46.0%)
2. Osteoporosis is more common in women than in men	True	$n = 173$ (91.5%)	$n = 16$ (8.5%)
3. There is a small loss of bone mass in the first 10 years after the onset of menopause	False	$n = 159$ (84.1%)	$n = 30$ (15.9%)
4. Osteoporosis increases the risk of bone fractures	True	$n = 178$ (94.2%)	$n = 11$ (5.8%)
5. Osteoporosis causes symptoms (e.g., pain) before possible fractures occur	False	$n = 77$ (40.7%)	$n = 112$ (59.3%)
6. A fall is a factor as important as the presence of low bone density in the occurrence of fractures	True	$n = 68$ (36.0%)	$n = 121$ (64.0%)
7. Starting at age 50, most women can expect at least one fracture over the next few years	True	$n = 146$ (77.3%)	$n = 43$ (22.8%)
8. Smoking can contribute to osteoporosis	True	$n = 134$ (70.9%)	$n = 55$ (29.1%)
9. High salt intake is a risk factor for osteoporosis	True	$n = 112$ (59.3%)	$n = 67$ (40.7%)
10. Any type of physical activity is beneficial for osteoporosis	False	$n = 52$ (27.5%)	$n = 137$ (72.5%)
11. An adequate intake of calcium can be obtained by drinking 2 glasses of milk/day	True	$n = 150$ (79.4%)	$n = 49$ (20.6%)
12. Moderate alcohol consumption has negative effects on the onset of osteoporosis	False	$n = 145$ (76.7%)	$n = 44$ (23.3%)
13. There are currently effective treatments for osteoporosis	True	$n = 186$ (98.4%)	$n = 3$ (1.6%)

participants. In terms of osteoporosis prevention practices and lifestyle behaviors, more participants reported using vitamin D supplements (38.6%) compared to calcium supplements (28.6%). Alcohol consumption was reported by a quarter (27%) of subjects, while caffeine consumption is much more frequent, being practiced by three quarters (76.7%) of participants. Less than one-quarter (21.7%) of respondents were current smokers. When it comes to daily physical activity, most respondents (45.5%) reported doing less than 30 min of exercise per day, while only 23.8% practice more than 60 min per day.

In our study group, the majority (77.2%) of participants reported not having undergone a DXA bone quality test, the main diagnostic approach for osteoporosis (Table 2). Only 28 subjects (14.8%) undertook such an investigation once, while very small percentages made DXA test two ($n = 7$, 3.7%), three ($n = 5$, 2.6%), four ($n = 2$, 1.1%), or five ($n = 1$, 0.5%) times. Analysis of participants groups presented in Table 5 revealed that women perform this test at a higher rate than men, with statistically significant differences between the sexes ($p = 0.03$). Patients with a history of fractures performed significantly ($p = 0.00$) more DXA test (40.8%) compared to those without a history (16.4%).

Out of the total number of subjects, 14.8% ($n = 28$) reported having an osteoporosis diagnosis, with the highest number of osteoporosis cases being in the 60–69 age group (57%, $n = 16$). However, 43% ($n = 12$) of individuals diagnosed with osteoporosis did not receive treatment. We then comparatively evaluated subgroups of individuals with and without osteoporosis (Table 6). There was a significant difference ($p = 0.002$) in the prevalence of the pathology across age groups, with the highest number of cases (26.7%, $n = 16$) recorded in individuals aged 60–69 ($n = 60$). The chi-square test yielded very high statistical significance for both comparisons ($p = 0.000$), indicating a strong association between osteoporosis diagnosis and the use of calcium and vitamin D supplements.

Lastly, we evaluated the effect of the history of certain co-associated pathologies (diabetes mellitus, hypo/hyperthyroidism, kidney problems, rheumatoid arthritis) and the use of proton pump inhibitors (PPI) on osteoporosis (Table 7). A significant higher prevalence ($p = 0.008$) of osteoporosis was recorded in patients having associated pathologies (25.5%) compared to respondents without co-morbidities (10.4%). Although osteoporosis diagnosis was more frequent in respondents taking proton pump inhibitors for more than 3 months than those who did not follow such chronic treatment (22.9% vs. 13.0%), the difference was not statistically significant. Also, no differences in the daily duration of exercise between diagnosed and undiagnosed individuals were registered. Conversely, patients suffering from associated pathologies were statistically more likely ($p = 0.036$) to have experienced falls (34.5%) compared to those without co-morbidities (20.1%).

Community 1 consists of 60 participants; its defining features are overweight BMI (1.17 times the overall network percentage), urban (1.41), and highly educated (2.13) participants, with no vitamin D supplements (1.86). The remaining features are irrelevant to the segregation of Community 1. We maintain the same description for the other communities. Community 2 includes 57 participants, characterized by mainly people aged 60–69 (1.58 times the average percentage) and 80–89 (2.4), males (1.34), urban (1.38) and lower educated (1.85), smokers (1.45) and coffee drinkers (1.45). Community 3, consisting of 34 participants, is characterized by participants aged between 70–79 (1.78 times the reference percentage), rural (3.35), lower educated (1.78), and engaged in physical activity more than 60 min daily (2.57), who tend to have fractures (1.29) and comorbidities (1.42), with osteoporosis (1.66), taking osteoporosis treatment (1.68), and with DEXA test (1.58). Community 4 includes 19 participants, and its most relevant features are age between 40–49 (2.96), rural (3.45), highly educated

TABLE 4 Differential analysis of osteoporosis knowledge level scores in groups of subjects.

Variable	Group	Group count (*n*=)	Mean of knowledge level	Standard deviation of knowledge level	*p*-value
Gender	Male	40	7.8	2.98	0.008*
	Female	149	9.2	1.87	
Age range	40–49	40	8.8	2.22	0.355
	50–59	58	9.1	1.71	
	60–69	60	8.9	2.16	
	70+	31	8.7	3.03	
Residency	Rural	58	9.2	2.24	0.259
	Urban	131	8.8	2.19	
Level of education	Secondary school	25	8.5	2.79	0.637
	High-school	76	9.1	2.17	
	Post-secondary school	22	8.7	1.86	
	University	66	8.9-	2.13	
Recent falls	No	143	8.8	2.33	0.231
	Yes	46	9.2	1.75	
Family history of osteoporosis	No	157	8.8	2.26	0.050*
	Yes	32	9.6	1.77	
Osteoporosis diagnosis	No	161	8.8	2.19	0.081
	Yes	28	9.6	2.20	
BMI	Underweight (<18.5 kg/m^2)	3	10.3	0.58	0.450
	Normal weight (18.5–24.9 kg/m^2)	51	9.0	2.40	
	Overweight (25–29.9 kg/m^2)	84	9.0	2.23	
	Obesity (>30 kg/m^2)	51	8.6	2.01	
Source of information	Physician	37	9.5	1.98	0.588
	Friends/family	36	9.0	1.60	
	Social networking	39	9.1	2.01	
	Others (radio/TV)	29	9.0	1.94	

*Statistical significance.

(2.13), smokers (1.23), coffee (1.23) and alcoholic beverages (1.23) drinkers, with no history of fractures (1.27) and comorbidities (1.26) and not having diagnosis of osteoporosis (1.17). Community 5 comprises 8 participants, all females (1.24 times the reference percentage), aged between 50–59 (2.76), urban (1.41) and lower educated (1.89), consuming calcium (3.52) and vitamin D supplements (2.52), engaged in more than 60 min of daily physical activity (1.56), with at least one DXA scan (1.67) and having treatment for osteoporosis (1.43). Community 6, the smallest community with five subjects, has as the main features participants aged 50–59 (3.21), underweight (24.39), urban (1.41) and with higher education (1.70), calcium (3.52) and vitamin D (2.65) supplements consumers, alcohol (2.66) and coffee (1.30) drinkers, smokers (1.30), with a history of fractures (3.18) and comorbidities (2.07), diagnostic of osteoporosis (7.04), DXA scanned (4.46) and osteoporosis treatment (6.86).

When investigating if there is any correlation or link between the communities from Figure 1 (described above) and the questionnaire results, we observe that the per-community distributions of results (values between 0 and 12) are similar to the overall distribution (see the histograms in Figure 2, where some of them are affected by the low number of participants). Accordingly, we cannot support any connection between the considered features—from the 4 feature classes—and the osteoporosis knowledge level revealed by the questionnaire results.

We provide a more detailed description of all communities in Supplementary Table S1.

4 Discussion

According to Eurostat projections, by 2060, the Romanian population over 65 years will reach 35%. Moreover, given the tendency of decreasing birth rate and the growing prevalence of CVDs, cancer, respiratory diseases, and other morbidities that require polymedication, an increase in the incidence of frailty syndrome among Romanian population is expected (31, 32). Yet, fragility research is still scarce in Romania (2). It is well-recognized that senescence plays an important role in the development of age-related osteoporosis and is directly tied to the rise in the number of frail

TABLE 5 Differential analysis of DXA test performance in groups of subjects.

Variable	Group	DXA test = no		DXA test = yes		*p*-value
		Count (*n*=)	%	Count (*n*=)	%	
Gender	Male	36	90.0%	4	10.0%	0.030*
	Female	110	73.8%	39	26.2%	
Residency	Rural	45	77.6%	13	22.4%	0.941
	Urban	101	77.1%	30	22.9%	
Level of education	Secondary school	18	72.0%	7	28.0%	0.506
	High-school	56	73.7%	20	26.3%	
	Post-secondary school	19	86.4%	3	13.6%	
	University	53	80.3%	13	19.7%	
Recent falls	No	112	78.3%	31	21.7%	0.535
	Yes	34	73.9%	12	26.1%	
History of fractures	No	117	83.6%	23	16.4%	0.000*
	Yes	29	59.2%	20	40.8%	

*Statistical significance.

TABLE 6 Differences in preventive practices and lifestyle behaviors between diagnosed and undiagnosed respondents.

Variable	Group	Osteoporosis diagnosis = no		Osteoporosis diagnosis = yes		*p*-value (chi square test)
		Count (*n*=)	%	Count (*n*=)	%	
Age-range	40–49	40	100.0%	0	0.0%	0.030*
	50–59	52	89.7%	6	10.3%	
	60–69	44	73.3%	16	26.7%	
	70+	25	80.6%	6	19.4%	
Daily physical activity	<30 min/day	77	89.5%	9	10.5%	0.284
	30–60 min/day	48	82.8%	10	17.2%	
	>60 min/day	36	80.0%	9	20.0%	
Calcium supplements	No	124	91.9%	11	8.1%	0.000*
	Yes	37	68.5%	17	31.5%	
Vitamin D supplements	No	108	93.1%	8	6.9%	0.000*
	Yes	53	72.6%	20	27.4%	

*Statistical significance.

people. Osteoporosis and CVDs are also closely linked: patients with low bone mineral density or increased bone turnover have a higher risk of frailty and therefore of cardiovascular morbidity and mortality. Thus, a multidisciplinary approach is needed in order to decrease the socio-economic burden, the iatrogenic-induced harm, the number of falls and hospitalizations in frail elderly people, and thus decrease the mortality rate (33). Our study aimed to increase clarity among healthcare providers about osteoporosis awareness in the Romanian population, with the objective of providing clear and targeted recommendations to address the identified gaps.

In terms of knowledge about osteoporosis, 75.1% of participants reported being aware of this pathology. The overall level of knowledge is moderate (9.0 ± 0.15), consistent with the findings of other studies (34–36). Compared to men, women tend to be better informed about the pathology. This gender gap has been previously documented and could be due to the misconception that osteoporosis is a women's disease (37–41). Thus, to avoid underdiagnosis among males, it is essential to raise awareness equally in both sexes (42, 43). In contrast to the findings of previous research studies, our sample shows no statistically significant differences in the level of knowledge among respondents based on their age decade, level of education, or residency (44–48). Unexpectedly, participants with a reported diagnosis of osteoporosis did not have a better knowledge score than those without a diagnosis. This finding is consistent with a study conducted in Poland and suggests that patients could benefit from more intensive therapeutical education, possibly offered by clinical pharmacists (49). A meta-analysis published in 2020 concluded that osteoporosis preventive education could also benefit adolescents in terms of long-term bone health behaviors (50). On the other hand, respondents with a family history of osteoporosis are better informed compared to those with no family history of osteoporosis. Although primary care specialists may be more inclined to provide more information to

TABLE 7 The effect of associated pathologies and the use of proton pump inhibitors on osteoporosis diagnosis and risk factors.

Variable	Group	Response = no		Response = yes		*p*-value
		Count (*n*=)	%	Count (*n*=)	%	
Osteoporosis diagnosis						
Associated pathologies	No	120	89.6%	14	10.4%	0.008*
	Yes	41	74.5%	14	25.5%	
PPI administration >3 months	No	134	87.0%	20	13.0%	0.138
	Yes	27	77.1%	8	22.9%	
Recent falls						
Associated pathologies	No	107	79.9%	27	20.1%	0.036*
	Yes	36	65.5%	19	34.5%	
PPI administration >3 months	No	117	76.0%	37	24.0%	0.834
	Yes	26	74.3%	9	25.7%	
History of fractures						
Associated pathologies	No	103	76.9%	31	23.1%	0.172
	Yes	37	67.3%	18	32.7%	
PPI administration >3 months	No	114	74.0%	40	26.0%	0.975
	Yes	26	74.3%	9	25.7%	

*Statistical significance; PPI, proton pump inhibitors.

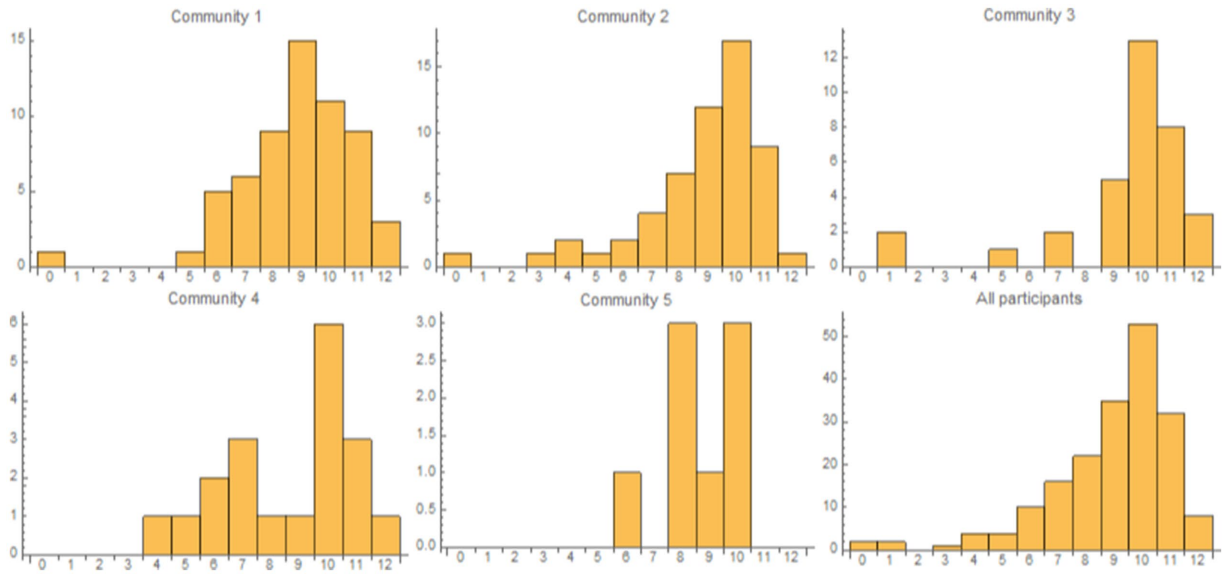

FIGURE 2
The panels present the histograms for the first 5 communities in network G and all participants, where the bins correspond to the questionnaire results values (0 to 12). We excluded Community 6 because it comprises only 5 vertices. The osteoporosis-knowledge questionnaire result distributions for each community are similar to the overall (i.e., all participants) distribution.

patients with a family background of osteoporosis (51, 52), 60.8% of our respondents reported that their GP did not inform them about the risk of developing osteoporosis, a concern also identified in other studies (53–55). Instead, the main source of information regarding osteoporosis identified in our study was social networking (27.7%), followed by physician (26.2%). Thus, the underdiagnosis of osteoporosis can also be attributed to the acquisition of incomplete or misleading information about the disease from unauthorized sources (56).

The analysis of the subjects' responses to each question assessing their level of knowledge yielded some concerning findings. Almost half of the respondents were unaware that a family history of osteoporosis increases the susceptibility to the disease, and nearly 60% considered that osteoporosis causes symptoms prior to a fracture

occurring. These results imply that patients may underestimate and underinvestigate the disease, leading to a delayed diagnosis that is often established after the occurrence of potentially disabling fractures. This is further corroborated by the high percentage of respondents (77.2%) who have never undergone at least one DXA test in their lifetime. What is more, 73.9% of our respondents reported recent falls. This could relate to the fact that 64.0% of participants believed that a fall is not as important as a decrease in bone mineral density in the occurrence of a fracture. Yet again, the DXA test is performed to a significantly higher extent by women than men, supporting the assumption that men tend to be underdiagnosed. Concerningly, a recent study in Romania showed that the number of DXA scans decreased by 37.8% after the COVID-19 pandemic compared to the previous year, increasing the burden of osteoporotic fractures (57–60). Taken together, our findings suggest DXA investigations are not frequently used, possibly indicating a reduced awareness of their importance or barriers in accessing them.

There is a noticeable tendency to disregard preventive strategies in the management of osteoporosis. Calcium and vitamin D play crucial roles in bone homeostasis. Additionally, vitamin D is pivotal in calcium metabolism, facilitating its absorption (13, 61). The general recommendations for calcium intake are 1,000 mg per day for males aged 19 to 70 and females aged 19 to 50. For males aged 71 and older and for women aged 51 and older, the daily calcium intake should be 1,200 mg (13, 15, 61). International Osteoporosis Foundation recommends a vitamin D intake sufficient to maintain a serum 25(OH)D level above 20 ng/mL, with daily doses of vitamin D ranging from 800 to 1,000 IU (31). Concerningly, in Europe, there is an inadequate intake of calcium and vitamin D in the elderly, predisposing these individuals to osteoporosis (4, 61). Our results showed statistically significant differences ($p = 0.000$) for calcium and vitamin D supplementation between respondents with a diagnosis of osteoporosis and healthy respondents, with individuals already diagnosed having a greater propensity to use such supplements to reach the target level. This leads to the conclusion that calcium and vitamin D supplementation is under-utilized as a preventive measure in the Romanian population. Moreover, the majority of individuals in our study are sedentary and overweight, 44.5% of respondents having a BMI between 25 and 30 kg/m^2. Only 23.8% of individuals reported engaging in physical activities for more than 60 min per day. A recent systematic review which included a total of 59 studies concluded that physical activity lasting more than 60 min 2–3 times/week for at least 7 months may improve bone mineral density in people 65 years old and over (14, 62). There is a positive correlation between osteoporosis knowledge and daily physical activity: respondents with higher knowledge scores tend to have a longer duration of daily physical activity (rho = 0.153, $p = 0.036$). Yet, despite the study population demonstrating moderate knowledge about osteoporosis and its risk factors, preventive measures were adopted to a limited extent, consistent with findings from other studies (40, 56, 63). Thus, the findings further underscore the necessity for both preventive and curative therapeutic education in order to enhance diagnosis rates and achieve effective management of the disease.

In our study, the overall prevalence of osteoporosis diagnosis was 14.8%. Compared with healthy subjects, respondents with associated comorbidities were more likely to experience recent falls ($p = 0.036$) or to have an osteoporosis diagnosis ($p = 0.008$), aligning with findings from previous investigations (2, 33). Alarmingly, 42.9% of respondents reported having osteoporosis did not undergo treatment, despite the fact that majority of participants stating that they were aware of effective osteoporosis treatments. In Romania, the number of individuals at high fracture risk who do not receive antiosteoporotic therapy is notably higher compared to the rest of the European countries. By 2034, a projected 15% increase in the number of fragility fractures is expected, negatively impacting the healthcare budget (15). Taking into consideration the costs per patient associated with osteoporotic fractures, Romania ranks last among the 29 European countries (15, 32).

Oral bisphosphonates (e.g., alendronate, zoledronic acid, risedronate, but not ibandronate) are recommended as the initial treatment in high-risk patients, with denosumab being considered an alternative therapy to reduce fracture risk. Teriparatide or abaloparatide for less than 2 years or romosozumab for 1 year should be the first line therapy for very high-risk patients (13, 64). Sequential therapy, involving initial treatment with a bone forming agent followed by an antiresorptive agent, are recommended to achieve better improvement in bone microarchitecture and increase BMD (13, 64). The reasons why patients at risk of fractures do not initiate antiosteoporotic treatment are numerous (1): insufficient information about the pathology and its treatment, resulting in a reduced perception of risk (2), the attitude of the general practitioner, who may lack confidence in treatment effectiveness or are concerned about potential side effects (3), reluctance towards medication, and (4) concerns regarding side effects (51, 65).

Given that osteoporosis is asymptomatic until the occurrence of the first fragility fracture (that happen even with minor trauma, such as fall from a standing position or a vertebral compression fracture incident), an efficient prevention strategy is the main key in reducing the incidence of fractures (16, 32, 66, 67). In both preventive and curative therapeutic patient education, the medical-pharmaceutical team (including physicians, nurses, pharmacists, clinical pharmacists, as well as physiotherapists, occupational therapists and dieticians) must collaborate for a more holistic approach to managing the disease. Thus, healthcare providers could achieve this goal by (1): increasing the number of informative and awareness campaigns (2), improving the identification of individuals at risk of osteoporosis (3), playing a more active role in counseling patients on supplements and promoting a healthy lifestyle (4), addressing non-adherence to medication (5), providing guidance on the proper use of anti-osteoporosis medication, and (6) reassuring patients about the benefits of the treatment and the risks associated with not taking it (68). Moreover, for patients with polypathology and consequently polypharmacy, there is a compelling need to review the therapeutic regimen to identify drugs that increase the risk of falls or may potentially induce osteoporosis over time (69–72).

The present study should be interpreted in the context of its strengths and limitations. The cross-sectional design of this study is a limitation because (1) it does not allow for the assessment of the long-term effects of osteoporosis knowledge level on osteoporosis prevention measures, and (2) osteoporosis incidence was not assessed longitudinally (3). Another limitation is the relatively small sample size, which might have negatively impacted the statistical power of certain results and (4) the limited number of patients >70 years old (aspect which will be addressed in further studies we plan to conduct on the frailty of Romanian patients). Moreover, the present findings are representative for the areas where the study was conducted and

cannot be generalized for the entire country. Despite these limitations, this study is the first attempt in Romania to assess the level of knowledge among the population regarding osteoporosis and its risk factors. Furthermore, a subsidiary purpose of the present study was to raise awareness regarding the disease and its complications. The importance of the study lies in its potential to identify relevant problems and improve both the diagnosis and the treatment rates of osteoporosis.

5 Conclusion

Taken together, the current work reveals a moderate level of knowledge about osteoporosis in conjunction with poorly osteoprotective practices. The growing number of elderly people in Romania, coupled with the high incidence of CVDs and the presence of multiple co-morbidities such as osteoporosis collectively increase the risk of developing frailty syndrome, the primary predisposing factor to disability. In this context, it is imperative to enhance awareness and knowledge about these diseases, and to implement appropriate management strategies for polypathologies and polymedication. This will contribute to improving the quality of life of Romanian patients and consequently reduce healthcare-related costs.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Ethics Committee of the "Victor Babes" University of Medicine and Pharmacy (no.47/2024). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

Author contributions

NJ: Conceptualization, Investigation, Validation, Writing – original draft. VB: Writing – review & editing. DC: Writing – original draft. CM: Formal analysis, Validation, Writing – review & editing. TO: Formal analysis, Validation, Writing – review & editing. MJ: Writing – review & editing. AT: Writing – original draft. MR: Writing – original draft. LU: Writing – original draft. VG: Writing – review & editing. MU: Writing – review & editing. AB: Writing – review & editing. CD: Writing – review & editing. MA: Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2024.1485382/full#supplementary-material

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