CATÓLICA
INSTITUTO DE CIÊNCIAS DA SAÚDE
LISBOA · PORTO

DOES COGNITIVE RESERVE REFLECT FRAILTY IN PREOPERATIVE PATIENTS WITH ≥ 65 YEARS?

Dissertação apresentada à Universidade Católica Portuguesa para a obtenção do grau de mestre em Neuropsicologia

Por

Alexandra Califórnia Mendes

Lisboa, 2023

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Sob Orientação de

Prof. Doutora Maria Vânia Silva Nunes

Prof. Doutora Raquel Lemos

Lisboa, 2023

“Para ser grande, sê inteiro: nada

Teu exagera ou exclui.

Sê todo em cada coisa. Põe quanto és

No mínimo que fazes.

Assim em cada lago a lua toda

Brilha, porque alta vive.”

- Ricardo Reis

List of Abbreviations

AD – Alzheimer's disease

BR - Brain Reserve

CF - Cognitive Frailty

CR – Cognitive Reserve

CRIq – Cognitive Reserve Index questionnaire

EFS - Edmonton Frail Scale

FI - Frailty Index

fMRI - Functional Magnetic Resonance Imaging

GDS-15 – Geriatric Depression Scale – 15

IQ – Intelligence Quotient

MoCA – Montreal Cognitive Assessment

POCD – Postoperative Cognitive Dysfunction

POD – Postoperative Delirium

SFT – Semantic Fluency Test

SPSS – Statistical Package for the Social Sciences

TeLPI – *Teste de Leitura de Palavras Irregulares*

TFI – Tilburg Frailty Indicator

TUG – Timed Up and Go

WAIS- III – Wechsler Adult Intelligence Scale III

WHO – World Health Organization

Resumo

Enquadramento Teórico: Nas últimas duas décadas, a população idosa submetida a cirurgias aumentou significativamente. Com uma parte substancial dos pacientes cirúrgicos a cima dos 60 anos, é crucial explorar formas melhores de prestação de cuidados, uma vez que estão em maior risco de desenvolver fragilidade e complicações pós-operatórias. Considerando que a fragilidade é um forte preditor dessas complicações, são necessários estudos adicionais sobre o impacto da fragilidade na cirurgia, incluindo a sua ligação com a reserva cognitiva. Estudos recentes sugerem que as dimensões da reserva cognitiva podem ter um impacto protetor não apenas nos resultados cognitivos, mas também nos níveis de fragilidade. Este projeto visa compreender a relação entre a reserva cognitiva e os níveis de fragilidade na fase pré-operatória, visto que um nível mais alto de fragilidade pode ser preditor de complicações durante e após a cirurgia.

Metodologia: A amostra não probabilística intencional deste estudo consistiu em 61 participantes elegíveis para cirurgia e cognitivamente saudáveis. Após uma breve entrevista clínica, foram administrados vários instrumentos para avaliar a Reserva Cognitiva e a Fragilidade, incluindo: o *Cognitive Reserve Index Questionnaire* (CRIq), o Teste de Leitura de Palavras Irregulares (TeLPI), o *Tilburg Frailty Indicator* (TFI) e a tarefa *Timed Up and Go* (TUG).

Resultados: As pontuações brutas do CRIq exibiram correlações negativas entre: CRI-Trabalho e TFI- Total, CRI- Trabalho e componentes psicológicos do TFI, CRI-Educação e componentes psicológicos do TFI, CRI- Tempos Livres e TUG, e CRI- Total e TUG.

Discussão: Acredita-se que a Reserva Cognitiva tenha um efeito protetor contra as mudanças cerebrais relacionadas com a idade. A literatura recente sugere que os proxies da CR também podem ter um impacto protetor nos níveis de fragilidade. Os resultados do presente estudo parecem sugerir que: 1) Possuir um trabalho com maior complexidade ao longo da vida leva a uma diminuição significativa da fragilidade em idade avançada; 2) níveis elevados de educação e cargos profissionais elevados ao longo da vida estão correlacionados com a presença de menos componentes psicológicos de fragilidade em idosos; 3) pacientes que têm mais atividades de lazer são menos propensos a desenvolver fragilidade; 4) pacientes com uma CR mais alta são possivelmente menos propensos a desenvolver fragilidade. Os resultados do presente estudo corroboram a literatura.

Conclusões: O presente estudo apresenta algumas evidências do impacto protetor que a CR parece ter nos níveis de fragilidade em pacientes pré-operatórios. São necessários estudos *follow-up* para investigar o grau de correlação entre a CR e a Fragilidade e de que forma essa relação pode ser benéfica para a prática clínica.

Palavras-chave: Reserva Cognitiva; Fragilidade; CRIq; TFI; TUG.

Abstract

Theoretical Background: In the past two decades, the elderly population undergoing surgery has increased significantly. With a substantial portion of surgical patients being over 60 years old, it is crucial to explore better ways to manage their care, as they are at higher risk of frailty and postoperative complications. Given that frailty is a strong predictor of these complications, there is a need for further research on the impact and management of frailty in surgery, including its connection to cognitive reserve. Recent studies have proposed that CR dimensions might have a protective impact not only in cognitive outcomes, but also on frailty levels. This project aims to understand the relationship between CR and the levels of frailty in the preoperative phase, since a higher frailty level is expected to predict complications during and after surgery.

Methodology: The non-probability purposive sample for this study consisted of 61 participants eligible for elective surgery and cognitively healthy. Following a brief clinical interview, several instruments were administered to assess Cognitive Reserve and Frailty, which included: the Cognitive Reserve Index Questionnaire (CRIq), the *Teste de Leitura de Palavras Irregulares* (TeLPI), the Tilburg Frailty Indicator (TFI), and the Timed Up and Go (TUG) task.

Results: CRIq raw scores exhibited negative correlations between: CRI- Work and TFI-Total, CRI- Work and psychological components of the TFI, CRI- Education and psychological components of the TFI, CRI- Leisure Time and TUG and CRI- Total and TUG.

Discussion: Cognitive Reserve is believed to have a protective effect against physiological and age-related changes in the brain. The ongoing discussion in this topic suggests that CR proxies might also have a protective impact on frailty levels. The results of the present study seem to suggest that: 1) having a job with higher complexity during lifespan reflects on a significant decrease in frailty in advanced ages; 2) high levels of education and high occupational attainments throughout life are correlated with the presence of less psychological components of frailty in the elderly; 3) patients that have more leisure activities are less prone to develop frailty; 4) patients with a higher CR are possibly less prone to develop frailty. The results of the present study corroborate the literature.

Conclusions: The present study presents some evidence of the protective impact that CR seems to have in the frailty level in preoperative patients. Follow-up studies are necessary to investigate the degree of correlation between CR and Frailty and in which ways this relationship can be beneficial for clinical practice.

Key Words: Cognitive Reserve; Frailty; CRIq; TFI; TUG.

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1. Introduction

The global phenomenon of population aging is promptly taking place, with the number of individuals aged over 65 years increasing from 461 million in 2004 to a projected 2 billion by 2050 (Clegg, Young, Iliffe, Rikkert & Rockwood, 2013). The segment of older adults is currently the fastest growing of the population worldwide and the expectancy is for the number to increase even more (Ristescu, Pintilie, Moscalu, Rusu & Grigoras, 2021). This substantial demographic change will be reflected profoundly on the organization and provision of healthcare and social services (Clegg et al., 2013).

Although the increase in average life expectancy is recognized as an important accomplishment, it has been verified that this increment leads to changes in the main causes of morbidity and mortality in the population (Crimmins, 2015). In the past two decades, the rate of population aging has been outpaced by the growth in the number of elderly individuals undergoing surgical procedures, which entail subjacent health concerns (Partridge, Harari & Dhesi, 2012). As most patients undergoing major surgery are over 60 years of age, it seems important to explore better ways to manage elderly patients, since these subjects present a higher risk of postoperative complications than their younger counterparts (Cappe, Laterre & Dechamps, 2022).

Among clinical risk factors in aged individuals is frailty, due to its negative impact on the prognosis of patients (Clegg et al., 2013; Cappe et al., 2022). According to WHO (2017), this condition is characterized by multisystem dysregulations, loss of homeostasis, decreased physiological capacity and incremented vulnerability to morbidity and mortality. Estimates indicate that between 25 and 50% of people over 85 years present this condition and, subsequently, have an increased risk of falls, disability, dependency and death (Clegg et al., 2013).

Another important aspect is that the presence of frailty is a good predictor of postoperative complications (Cappe, Laterre & Dechamps, 2022). Nonetheless, the evaluation of this construct outside the geriatric context is reduced. In result, the evidence on the impact and management of frailty in surgery is insufficient and needs further studies (Cappe, Laterre & Dechamps, 2022).

Additionally, regarding brain frailty during aging, the emergence of diminished neurophysiological reserves and the connection to the onset of neurodegenerative diseases in later life, as well as their association with physical frailty, remains limited (Kelaiditi et al., 2013). This increase in the risk of acquiring neurodegenerative diseases constitutes another problematic manifestation of population aging (Crimmins, 2015). Over the last decades, the concept of Cognitive Reserve (CR) has been studied as a potential protective factor against the onset of age-related cognitive decline and functional impairments (Sardella, Catalano, Lenzo, Bellone, Corica, Quattropani & Basile, 2020). Recent studies have proposed that CR dimensions (e.g., occupation, leisure activities) might have a protective impact not only in cognitive outcomes, but also on frailty levels (Sardella et al., 2020).

Therefore, these introductory notes provide some insight regarding the need for more research on the elderly surgical population as it rises rapidly, as well as the urge to better understand protective factors that can prevent postoperative adverse outcomes.

2. Literature Review

2.1. Cognitive Reserve

2.1.1. The Concept of Reserve

The concept of reserve was described for the first time in the late 1980s, after Katzman and his colleagues (1989) performed a post-mortem analysis of the brains of 10 cognitively normal elders and discovered advanced Alzheimer's disease (AD) pathology (Stern, 2002). After repeated postmortem observations of subjects who managed to resist brain damage without exhibiting clinical symptoms and loss of functionality, it became clear that the accumulation of brain pathology does not have a narrow and direct relationship with the manifestation of cognitive and/or behavioral deficits (Tucker & Stern 2011; Nucci, Mapelli & Mondini, 2012).

Indeed, it was verified that some subjects do not display cognitive impairment through lifespan regardless of fulfilling neuropathologic criteria for neurocognitive disease, suggesting that the presence of pathology does not predict dementia at a functional level (Liu, Cai, Xue, Zhou & Wu, 2012).

To explain these differences among individuals in their ability to cope with physiological or pathological cognitive decline, various concepts and models of reserve were proposed (Stern, 2002).

2.1.2. Brain Reserve: Definition and Passive Model

The first theory that emerged encompassed the concept of Brain Reserve (BR). BR uses quantitative measures such as the size of the brain, the number of neurons or the number of synapses as proxies of reserve (Steffener & Stern, 2011; Stern, 2012). Regarding the BR framework, subjects with more brain reserve will require more brain damage to reach the threshold at which cognitive and behavioral deficits become apparent (Tucker & Stern 2011).

The contribution of BR was evidenced in several studies that reported that the incidence of dementia was lower in individuals with larger brains than in individuals with smaller brains (Katzman et al., 1989), as larger brains have more neural substrates to support normal function and slow the incidence of clinical manifestations (Steffener &

Stern, 2011). Another aspect to emphasize is that despite the level of pathology accumulated, subjects with more BR tend to have better clinical outcomes (Tucker & Stern 2011).

Underlying the construct of BR, the **passive model of reserve** was developed. In this model, the subject's capacity to cope with brain insult is determined by quantitative factors, as individuals with a larger brain size and increased number of neurons might be able to cope with more pathology and increased loss of neuronal count before clinical symptoms appear (Stern, 2012; Harrison et al., 2014; Stern, Barnes, Grady, Jones & Raze, 2019). Furthermore, this can explain how similar levels of brain pathology between two individuals can lead to distinct functional outcomes (e.g., two subjects with resembled levels of AD pathological deposition can have exceedingly different performances in neuropsychological tests) (Barulli & Stern, 2013). This conceptualization of BR is considered passive, because it implies that discrepancies in disease management are explained by relatively static features of the brain and does not acknowledge that individuals have uneven cognitive capacities (Stern, 2009; Harrison et al., 2014). In addition, this model is also seen as a threshold model, as when brain damage decreases BR to a certain threshold, loss of functional capacity becomes evident (Barulli & Stern, 2013).

While the initial conception of BR was purely quantitative, recent research has shown that this construct is more heterogeneous (Steffener & Stern, 2011). Recent studies regarding this matter have found a small correlation between IQ and brain volume (McDaniel, 2005), as well as the evidence that stimulating environments correlate with an increased neurogenesis and neurons growth (Brown, Cooper-Kuhn, Kempermann, Van Praag, Winkler, Gage & Kuhn, 2003).

2.1.3. Cognitive Reserve: Definition and Active Model

According to Stern (2002, 2003, 2009), **Cognitive Reserve** (CR) corresponds to the cognitive capacity to cope with brain pathological or physiological cognitive decline due to the presence of pre-existing neural pathways that use compensatory mechanisms. This construct, that is based on the plasticity of the brain, is believed to counter the effects of aging or brain injury (Nucci et al., 2012; Kang et al., 2011) and as a result can be seen as a protective brain factor (Chapko, McCormack, Black, Staff & Murray, 2017).

Therefore, individuals with higher CR will have better clinical outcomes (Tucker & Stern 2011) and will be able to resist to more age and disease-related changes through the effective and flexible use of resources, such as compensatory strategies and brain networks (Stern, 2002; Nucci et al., 2012; Lee et al., 2020). This means that individuals with higher CR will need more pathological changes to reach a clinical threshold and will be able to delay the manifestation of clinical symptoms (Tucker & Stern, 2011; Garba, Grossberg, Enard, Jano, Roberts, Marx & Buchanan, 2020).

CR represents an active form of reserve in which cognitive function is the relevant variable on behalf of brain size (Harrison et al., 2014). The interindividual differences in managing brain changes or pathology are linked to the effective or ineffective use of cognitive processes (Stern, 2012; Harrison et al., 2014; Stern & Barulli, 2019). In this point of view, the ability to utilize alternative preexisting cognitive processes is essential to explain the variation between a functionally debilitated individual and a functionally independent individual, despite equal brain insult (Stern, 2012; Stern & Barulli, 2019).

It is important to highlight that, in contrast with BR theory, CR hypothesis also takes into consideration brain related structural measures, although it suggests that it is possible to predict the risk of cognitive decline through independent measures of physical or biologic markers (Stern & Barulli, 2019). Furthermore, this theory is considered "*active*" for two reasons: 1) it attributes functional discrepancies between subjects to neuronal activity; and 2) it proposes that neural activity later in life is supplied by distinct cognitive exposures, experiences and activities engaged throughout the lifespan (Stern & Barulli, 2019). Some of these activities, beyond increasing cognitive capability, also shape CR, which in turn can decrease the risk of dementia in advanced ages (Scarmeas & Stern, 2003).

Regarding CR construction over time, cognitive processes can become different towards capacity, efficiency, and flexibility (Stern & Barulli, 2019). In this sense, CR is built over the relationships between several lifetime exposure factors (e.g., experiences, cognitive and intellectual activities) that can originate a more resilient brain to damage and pathology through the development of neural subtracts (Stern, 2002; Nucci et al., 2012; Garba et al., 2020).

On this regard, these two constructs (i.e., BR and CR) are not mutually exclusive and are proposed to operate at different levels: BR as a more static perspective that focuses on the **quantity** of available brain resources, and CR as a more dynamic perspective suggested to concern the **quality** of these resources and the possibility for brain adaptation (Menardi, Pascual-Leone, Fried & Santarnecchia, 2018). In this context, CR can be viewed as a flexible and efficient use of the available BR (Tucker & Stern 2011).

2.1.4. Cognitive Reserve: Neural Substrates/Mechanisms

According to functional neuroimaging studies, two neuronal mechanisms have been proposed to contribute to CR: neural reserve and neural compensation (Stern, 2012).

Neural reserve refers to the different levels of resilience of pre-existing cognitive networks to brain damage across individuals (Stern, 2012; Lee et al., 2018) and is related to prior brain capacity to cope with changes in aging or pathology (Siedlecki, Stern, Reuben, Sacco, Elkind, & Wright, 2009). The key idea of this mechanism is that discrepancies in capacity, efficiency and flexibility of cognitive resources occur due to differences in life experiences that can enhance or weaken neuronal network connections (Stern, 2006; Stern & Barulli, 2019).

On this regard, individuals with higher neural reserve seem to have more efficient cognitive grids (i.e., that require less activation than less efficient networks to execute the same task in a similar performance level), higher capacity networks (i.e., that can achieve a higher rate of activation relying on task difficulty) or higher flexibility (i.e., greater selection of compensatory brain networks) (Barulli & Stern, 2013). Alongside this mechanism arises the concept of **neural compensation**, that is responsible for the recruitment of compensatory networks when pathology deteriorates the main task-related network (Lee et al., 2018). Therefore, some subjects might be better than others in using alternative areas of the brain that were not previously utilized to compensate for cognitive loss (Siedlecki et al., 2009).

Recent research using functional Magnetic Resonance Imaging (fMRI) discovered activation of additional areas in older adults that are absent in younger adults, which were interpreted as secondary or compensatory brain regions (Steffener & Stern, 2012; Stern & Barulli, 2019).

In theory, the activation of these compensatory areas would provide an opportunity for older adults to perform as well as younger individuals. However, in practice, the opposite has been observed, as recruitment of alternative networks was associated with poorer performances (Craik & Bialystok, 2006; Steffener & Stern, 2012). Once the secondary recruited network is meant to ensure the functions of the damaged primary network, it is deemed that this compensatory mechanism has not been effective (Stern & Barulli, 2019). According to Stern and Barulli (2019, p. 184), "*alternative network acts as a cane to a pair of legs; it allows one to walk, but not nearly as well*".

2.1.4. Cognitive Reserve: Proxies and Measurement

As mentioned previously, CR is based on the idea of storage of resources and is believed to depend on the cognitive capabilities acquired during lifetime (Tucker & Stern, 2011; Nucci et al., 2012) in conjunction with constant brain activity (Garba et al., 2020). In line with this arises the prospect that CR is a modifiable factor that can be enhanced through cognitive, mental, and physical stimulating activities to postpone cognitive deterioration (Nucci et al., 2012; Tucker & Stern, 2011; Lee et al., 2020).

Notwithstanding the reach of a certain degree of consensus on the definition of CR, there is still an ongoing discussion about the proxies thought to contribute to this construct, the best methods to assess it, and their weighted contribution (Harrison et al., 2015; Kartschmit, Mikolajczyk, Schubert & Lacruz, 2019).

Regarding this topic, several standard proxies have been used to measure CR, such as years of education (Stern, 2006; Chapko et al., 2018; Garba et al., 2020), degree of literacy (Tucker & Stern 2011; Harrison et al., 2015), premorbid intelligence quotient (IQ) (Jones et al., 2011; Garba et al., 2020), complexity of occupational attainment (Stern, 2006; Garba et al., 2020), involvement in leisure activities (Scarmeas et al., 2001; Tucker & Stern, 2011; Garba et al., 2020), and the maintenance of social networks (Tucker & Stern 2011; Lee et al., 2020).

Education (total number of years) is one of the first proxies that arose in research and is currently considered one of the most reliable proxies of CR (Nucci et al., 2012), as a significant number of studies across the literature documented a significant correlation between a higher level of education and a better global neuropsychological function (Lee et al., 2020). In addition, studies in older adults with higher levels of education demonstrated slower rates of cognitive decline (Stern, 2009), reduced risk of mild cognitive impairment (Liu, Cai, Xue, Zhou & Fangping, 2013) and reduced risk of dementia (Harrison et al., 2015). Thereby, it is possible to conclude that education has a role in the normal and pathological cognitive deterioration or brain injury (Nucci et al., 2012).

Another well-known standardized measure of CR is premorbid intelligence (i.e., intellectual ability before brain damage occurs), that can be distinguished in fluid intelligence (i.e., reasoning, problem-solving) and crystalized intelligence (i.e., ability to use knowledge and skills) (Harrington et al., 2018). During the process of aging, the decline in fluid intelligence and the maintenance of a relatively stable crystalized intelligence is characterized as a normal trajectory (Harada, Love & Triebel, 2013). According to Harrington and colleagues (2018), AD proteins were found to be related with increased age-related decline in fluid intelligence, but not crystallized intelligence. The discrepancy score between fluid and crystallized intelligence is thought to have some evidence on AD related changes. Whereas crystallized intelligence is deemed to estimate the subject's intellectual capacity before decline and fluid intelligence represents the current level of intelligence (Harrington et al., 2018).

Therefore, intellectual decline is classified to have occurred when performance on fluid intelligence measures is lower than performance on crystallized intelligence measures (Harrington et al., 2018). Nowadays, there are several instrument options for estimating the discrepancy between these two types of intelligence, such as the *Teste de Leitura de Palavras Irregulares* (TeLPI). The TeLPI is a neuropsychological instrument, validated for the Portuguese population, that allows obtaining an individual's premorbid IQ (i.e., performance exhibited on the test reflects the crystalized intelligence) and the comparison with the expected IQ for that subject's level of education (i.e., fluid intelligence) (Alves, Simões & Martins, 2012; Alves, 2013; Alves, Martins & Simões, 2018). This instrument is particularly useful when there is no assessment of intelligence prior to the decline or brain insult or in cases where it is necessary to comprehend if cognitive decline is occurring (Alves, Simões & Martins, 2012; Alves, 2013; Alves, Martins & Simões, 2018).

In addition, individuals with higher levels of intelligence, education and socioeconomic status are more prone to experience an active lifestyle, which in turn contributes to the maintenance of verbal intelligence in later life (Scarmeas & Stern, 2003).

Besides the level of education and intellectual ability, premorbid engagement in leisure activities and complexity of occupational attainment also seem to provide an increase in CR (Nucci et al., 2012). A prospective study performed on 1772 old individuals (≥ 65 years), demonstrated a negative association between engagement in leisure activities and incidence of dementia, since subjects with high leisure activity exhibited 38% less risk of developing dementia (Scarmeas, Levy, Tang, Manly & Stern, 2001). In this research, a total of 13 leisure activities were considered, some examples being: reading books/newspaper, playing cards/games/bingo, volunteer work, visiting friends/relatives and physical exercising (Scarmeas et al., 2001).

Additionally, a recent study conducted by Kleineidam and colleagues (2022), provided evidence of an association between work related cognitive requirements (i.e., complexity of occupational attainment) and CR. This research concluded that seeking stimulating work environments could contribute to increased resistance to pathologies in later life, and that preventive measures against cognitive decline in old age might be complemented by a stimulating profession (Kleineidam at al., 2022).

In light of these considerations, all of the above-mentioned indicators are believed to contribute to CR, but their weighted influence has not been clearly defined (Stern, 2006; Harrison et al., 2015). Since CR is a multifaceted construct influenced by a plethora of components, utilizing a single indicator might not be an accurate measure (Kartschmit, Mikolajczyk, Schubert & Lacruz, 2019). In order to properly measure this construct, researchers developed combinations of the main socio-behavioral CR proxies in standardized questionnaires (Kartschmit et al., 2019). In turn, these standardized questionnaires, besides including numerous CR composites, provided a single score that allowed comparison of results among different studies (Kartschmit et al., 2019).

Regarding this standardized questionnaires, Cognitive Reserve Index questionnaire (CRIq) has been considered a reliable tool for CR measuring across research in the last decade (Garba et al., 2020). CRIq is a semi-structured questionnaire that encompasses 3 CR proxies aforementioned: education, work and leisure activities (Nucci et al., 2012). This instrument, not only enables the acquisition of 3 scores linked to the 3 proxies, but also the achievement of a single score of CR (Nucci et al., 2012) which can lead to standardization and measurement consensus in this matter.

Determining the importance and relevance of CR and the indicators that supply the reserve (e.g., modifiable indicators such as involvement with leisure activities) could lead to new intervention strategies to reduce the risk of cognitive impairment and dementia (Harrison et al., 2015). For this reason, there is a need to raise more awareness about the importance of engaging in cognitive activities and to create interventions that focus on promoting CR buildup from an early age onwards (Garba et al., 2020).

2.2. Frailty

2.2.1. Frailty: Context and Definitions

The concept of **frailty** involves a dynamic and multidimensional condition present in the normal aging process (Uslu & Canbolat, 2021) and can be characterized by a diminished function in numerous physiological systems, a loss of biological reserve in response to stressors (Mandelblatt et al., 2013; Oliveira, et al., 2020) and consequent dependency in activities of daily living (Uslu & Canbolat, 2021). As the process of aging takes place, there is a concurrent accumulation of damages in the cellular process, incremented vulnerability to illness, loss of compensatory mechanisms and increase in the level of frailty (Mandelblatt et al., 2013).

Physiological changes associated with frailty do not always achieve disease status, which means that some people (more commonly the elderly) can be frail without having a life-threatening illness (Rockwood & Mitnitski, 2007). Some of the changes include disability, physical and cognitive impairments, psychosocial risk factors and geriatric complications (such as falls, delirium and urinary incontinence) (Kelaiditi et al., 2013).

Based on this framework, two distinct definitions were proposed.

In the first and most used definition, proposed by Fried and colleagues (2001), an individual is considered "frail" if three out of five of the following criteria are met: slow speed gait, low physical activity, high self-reported exhaustion, involuntary weight loss (≥4.5 kilograms over 12 months) and low grip strength. In this perspective, frailty can be viewed as a decline of reserves (health, physical ability and cognitive capacity) that gives rise to vulnerability (Rockwood & Howlett, 2018).

In another perspective, proposed by Mitnitski and colleagues (2001), frailty can be represented by the number of health deficits accumulated across the adult life course (Mitnitski, Song & Rockwood, 2013). Regarding these acquired health problems, they may have small effects on quality of life when considered in isolation, however, their cumulative effect becomes significant (Mitnitski, Mogilner & Rockwood, 2001; Rockwood & Mitnitski, 2007; Mitnitski, Song & Rockwood, 2013). It is also important to refer that the number of health problems tends to increase with aging, leading to the consequent increment in frailty (Mitnitski, Song & Rockwood, 2013).

Initially, this phenotype of aging did not include cognitive domains although it is now considered one of the key factors involved in frailty (Mandelblatt et al., 2013). Recently, it was discovered that, not only individuals with frailty have higher risk of developing cognitive disease, but also that these patients are more vulnerable to cognitive deficits after stressors (Mandelblatt et al., 2013). In line with this, numerous studies conducted among older subjects (≥ 65 years), demonstrated that cognitive performance is correlated with measures of frailty (Ávila-Funes et al., 2009; Yassuda et al., 2012; Arai, Satake & Kozaki, 2018).

Alongside this notion, the International Academy of Nutrition and Aging (IANA) and the International Association of Gerontology and Geriatrics (IAGG) conceived the term "**Cognitive Frailty**" (CF) to describe a heterogeneous clinical condition characterized by the concurrent presence of physical frailty and cognitive impairment (Kelaiditi et al., 2013; Arai, Satake & Kozaki, 2018). The presence of dementia and cognitive impairment due to neurodegenerative disorders was defined as exclusion criteria for this condition (Kelaiditi et al., 2013).

Later, two subtypes of cognitive frailty were suggested: the reversible CF (presence of physical frailty or pre-frailty and subjective cognitive decline) and the potentially reversible CF (presence of physical frailty or pre-frailty and objective cognitive impairment) (Ruan, Chen, Bao, Li, & He, 2015). Presently, the definition of CF has not reached a consensus and needs further discussion (Arai, Satake & Kozaki, 2018).

Concerning its **prevalence**, a recent systematic review that compiled 21 community cohort studies and a comprehensive sample of 61500 elder people concluded that frailty is present in 4% to 59% of the healthy elderly population (Collard, Boter, Schoevers & Voshaar, 2012; Clegg et al., 2013; Uslu & Canbolat, 2021). This considerable interval of percentages might be explained by the different operationalizations of frailty and the inclusion and exclusion criteria considered (Clegg et al., 2013). Other aspects to be emphasized are that frailty seems to be more prevalent in women (9.6%) than in men (5.2%), and steadily increases with age (4% in 65-69 years, 7% in 70-74 years, 9% in 75-79 years, 16% in 80-84 years and 26% in ≥85 years) (Collard et al., 2012; Clegg et al., 2013). This statistic reinforces the importance of screening this phenotype. At the same time, old frail patients are more prone to a lower quality of life, a higher incidence of fatigue and reduced physical and cognitive abilities when compared to non-frail patients (de Arruda et al., 2019; Uslu & Canbolat, 2021).

Additionally, it is important to highlight that frailty is not static, which means that its severity fluctuates in time and is modulated by different cognitive and physical activities. Therefore, it can be lessened through interventions, such as exercise-based interventions (Oliveira et al., 2020).

2.1.2. Frailty: Phenotype and Deficit Accumulation Models

The acceptance of the concept of frailty led to the emergence of a variety of definitions and perspectives that remain currently under debate (Theou, Walston & Rockwood, 2015). According to the literature, two main approaches to conceptualize this construct have arisen: the phenotype model and the deficit accumulation model (Theou, Walston & Rockwood, 2015).

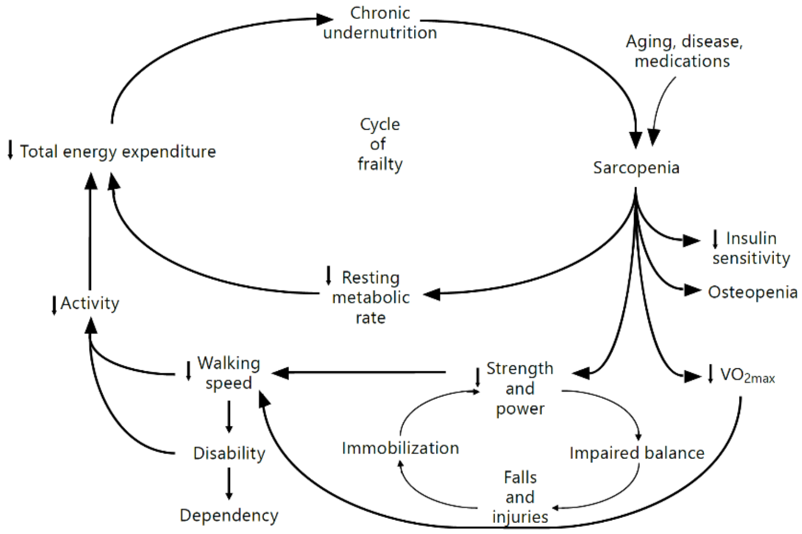
The **frailty phenotype model** sees frailty as a biological syndrome, based on signs and symptoms that are commonly seen among vulnerable older adults, such as weakness, fatigue, or weight loss (Theou, Walston & Rockwood, 2015). Indeed, this perspective suggests the existence of a relation between frailty criteria defined by Fried et al. (2001) (i.e., unintentional weight loss, low grip strength, exhaustion, low physical activity, and slow speed gait) and the vulnerability to adverse outcomes (i.e., increased number of falls, mobility degradation, hospitalization, or mortality) (Partridge et al., 2012; Clegg et al., 2013).

In other words, this approach connects the cumulative declines across multiple physiologic systems (low energy expenditure, low physical activity, poor nutritional intake, and loss of skeletal muscle) with a cycle of disability and functional decline (Walston & Fried, 1999; Fried et al., 2001). In this cycle, these interconnected domains reinforce each other and can lead to a decline in other essential physiological systems (Walston & Fried, 1999).

Other factors associated with functional deterioration and disability, such as cognitive impairment, were not considered as a component in this model, which prompted some criticism (Clegg et al., 2013). Nevertheless, the clusters of variables contemplated in the phenotype model were independently validated and can reliably predict frailty levels (Clegg et al., 2013).

Figure 1.

The Cycle of Frailty.



Source: Fried et al., 2001.

On the other hand, the **deficit accumulation model** categorizes frailty as a multidimensional risk state that can be measured by the quantity of health deficits on behalf of the nature of these problems (Theou, Walston & Rockwood, 2015). According to this model, linked to the perspective of Mitnitski et al (2001), the exponential increase in the number of health problems with age is related to the exponential increase in recovery time and, consequently, influences the system's ability to repair damage (Mitnitski, Song & Rockwood, 2013). Thus, a higher number of deficits will be linked to a higher probability of frailty and a greater risk of adverse health outcomes (Theou, Walston & Rockwood, 2015).

This model also conveys the relevant idea that frailty is a gradable variable rather than a present/absent condition, as it is the number of equally weighted insufficiencies associated with negative outcomes, instead of specific clusters of deficits (Clegg et al., 2013).

2.2.3. Frailty: Proxies and Measurement

There are several issues regarding the operationalization of frailty, namely the lack of a universally accepted definition, the different reasons behind the measurement of this construct (i.e., screening, assessment, prediction of prognosis), the different tools used by different health professionals, and the fact that its measurement has been used mainly in the research field (Partridge et al., 2012). Considering the latter, the clinical assessment of frailty is at a starting point (Partridge et al., 2012).

In terms of measurement, specific physiological changes and impairments have been used as proxies in frailty, such as deterioration in mobility, balance, muscle strength, endurance, physical activity, cognition, and nutrition (Clegg, Young, Iliffe, Rikkert & Rockwood, 2013; Theou, Walston & Rockwood, 2015).

Deterioration in mobility and muscle strength have been operationalized through simple standardized gait speed tests, such as Timed Up and Go (TUG) and hand grip strength mensuration using a hand dynamometer (Clegg et al., 2013). These two measures (i.e., slow gait speed and hand grip strength) have been explored as reliable single assessments to detect frailty and several studies have shown associations between these variables and adverse outcomes, such as higher risk of falls, disability, hospitalization, and mortality (Veronese, Stubbs, Volpato, Zuliani, Maggi & Cesari, 2018; Bohannon, 2019).

Currently, various instruments are being used to measure the phenotype of aging though a combination of these proxies, some examples being the Tilburg Frailty Indicator (TFI), the Frailty Index (FI) and the Edmonton Frail Scale (EFS) (Dent, Kowal & Hoogendijk, 2016).

The TFI is self-report questionnaire that contains 15 items concerning 3 main domains of frailty: physical, psychological, and social (Gobbens et al., 2010; Theou, Walston & Rockwood, 2015). The physical components of this questionnaire have shown good predictive properties in regard to adverse outcomes (Dent, Kowal & Hoogendijk, 2016).

The FI, linked to the definition and model suggested by Mitnitski et al (2001), involves the accumulation of 30 or more health deficits and is based in the notion that a higher number of health comorbidities indicates higher frailty (Dent, Kowal & Hoogendijk, 2016). These health conditions encompass any comorbidity, a lessened ability to perform activities of daily living, a poor nutritional status, an impaired physical status, a lower level of cognition and a more pessimistic health attitude in general (Joseph, Pandit, Sadoun, Zangbar, Fain, Friese, & Rhee, 2014).

Lastly, the EFS is a useful instrument for the identification of this construct in hospital settings (Dent, Kowal & Hoogendijk, 2016). Concerning the scoring, EFS has a total of 17 points and assesses 9 domains: cognition, general health status, self-reported health, functional independence, social support, polypharmacy, mood, continence, and functional performance (Theou, Walston & Rockwood, 2015; Dent, Kowal & Hoogendijk, 2016).

However, it is important to emphasize that none of the proposed instruments/proxies provide a definitive diagnosis of frailty (Theou, Walston & Rockwood, 2015). Therefore, recent literature highlighted the need for a standard measurement of this condition, as it would enable consistent recognition of frailty in the context of clinical practice and research (Dent, Kowal & Hoogendijk, 2016). To successfully achieve it, the standard measurement should have the capacity to accurately and reliably identify frailty, anticipate adverse clinical outcomes, foresee patient response to potential interventions, and monitor outcomes of treatments in frail people (Clegg et al., 2013; Dent, Kowal & Hoogendijk, 2016). Additionally, it must be supported by a biological theory and must be simple to apply (Dent, Kowal & Hoogendijk, 2016). Forthcoming steps must be towards identifying the most suitable frailty instrument for clinical and/or research purposes (Dent, Kowal & Hoogendijk, 2016).

In this matter, diverse geriatric interventions are being developed to lessen the effects of frailty in the elderly population. However, the absence of a standardized and valid screening method has been the major obstacle (Fried et al 2001). In this sequence, health care professionals should do whatever possible to detect this condition at an early phase in elderly patients (Uslu & Canbolat, 2021; Ristescu et al., 2021).

2.2.4. Frailty: Surgical Population

Regarding the older surgical populations, frailty has been identified as a risk factor for increased disability, loss of independence, morbidity, mortality, prolonged hospital stays, and diminished quality of life (Makary et al., 2010; Partridge et al., 2012). The preoperative moment is known to be a strikingly vulnerable period for most elderly patients (Ristescu et al., 2021; Uslu & Canbolat, 2021), as around 42% to 50% of this population exhibits frailty (Makary et al., 2010; Partridge et al., 2012).

The preoperative assessment of frailty is crucial to fully inform the patient about the risks of undergoing surgery and optimize modifiable factors to improve the patient's expectancy of a successful outcome (Partridge et al., 2012; Revenig et al., 2013).

Due to the subjectiveness of the decision of whether or not a patient will tolerate a surgical intervention, an objective assessment is crucial for decisions of the surgical team, especially in the elderly and/or comorbid population (Revenig et al., 2013). Factors such as low functional reserve and level of aggressiveness of the forthcoming surgery entail a larger liability for postoperative complications and mortality (Ristescu et al., 2021). Postoperative cognitive complications, such as postoperative delirium (POD) and postoperative cognitive dysfunction (POCD), are common among elderly patients who have undergone significant surgical procedures (Monk & Price, 2011).

Besides the low functional and physical reserve, because frailty is a dynamic and multidimensional condition, the hypothesis that CR proxies might have a protective impact not only on cognitive trajectories, but also on frailty, has been increasingly debated in recent studies (Sardella et al., 2020).

2.2.5. Objectives and Question of Interest

This project aims to understand the relationship between CR and the levels of frailty in the preoperative phase, since a higher frailty level is expected to predict complications during and after surgery.

Therefore, the main question of interest is: *Is **cognitive reserve** associated with the level of **frailty** in the preoperative moment, in subjects ≥ 65 years of age?*

3. Methodology

3.1. Study Design and Hypothesis

This project has a **prospective correlational design**, as it will have one assessment moment in the preoperative period. Thus, we can formulate the research hypothesis, based on the literature described above:

Main Hypothesis: Higher cognitive reserve will be associated with a lower level of frailty in preoperative conditions.

In order to operationalize the main hypothesis, four specific hypotheses will be analyzed in this study:

Hypothesis 1: Higher scores in CRIq will be associated with lower scores in TFI.

Hypothesis 2: Higher scores in CRIq will be associated with lower scores in TUG.

3.2. Participants and Sampling Process

The sample of this project is composed by **61 patients**, eligible for elective surgery, therefore representing a non-probabilistic purposive sample. The vast majority of the sample had an oncological disease.

To be included, patients needed to meet the following requirements: (**1**) Age ≥ 65 years; (**2**) Native European Portuguese speaking; (**3**) Absence of visual or hearing impairment after correction (i.e., wearing eyeglasses or hearing aids); (**4**) Elective surgery (breast, abdominal, urological, thoracic or gynecological); and (**5**) Preoperative anesthesia evaluation.

Patients were excluded if any of the following criteria were met: (**1**) Psychiatric comorbidities, or neurologic diagnosis; (**2**) Low scores in screening instruments (i.e., MoCA, SFT and GDS- 15), considering the age and education of the participant; (**3**) Schooling abroad; or (**4**) Emergency surgery.

3.3. Instruments

The preoperative assessment had an approximated time of 45 minutes to 1 hour, and included the following instruments, implemented in the respective order: the Tilburg

Frailty Indicator (TFI), the Montreal Cognitive Assessment (MoCA), the Semantic Fluency Test (SFT), the *Teste de Leitura de Palavras Irregulares* (TeLPI), the Cognitive Reserve Index questionnaire (CRIq), the Geriatric Depression Scale (GDS-15) and the Timed Up and Go (TUG) test.

The level of **frailty** was determined through the Tilburg Frailty Indicator (TFI) and the Timed Up and Go (TUG). Furthermore, the evaluation of **cognitive reserve** was estimated through the Cognitive Reserve Index questionnaire (CRIq) and the *Teste de Leitura de Palavras Irregulares* (TeLPI). To screen **cognitive impairment** in the preoperative assessment, Montreal Cognitive Assessment (MoCA) and the Semantic Fluency Test (SFT) were applied. Lastly, the Geriatric Depression Scale (GDS-15) was used to screen for **depression**.

3.3.1. Tilburg Frailty Indicator (TFI)

The **TFI** (part B) is a self-reported questionnaire composed of 15 items focused on the 3 main domains of frailty: physical, psychological, and social (Gobbens et al., 2010; Coelho et al., 2015). It is composed by 8 physical health questions (weight loss, overall physical health, difficulty in walking, balance, vision problems, hearing problems, hand strength, and tiredness), 4 psychological health questions (cognition, depressive symptoms, anxiety, and coping) and 3 questions regarding social activity (living alone, social relationships and social support).

The estimated duration of this assessment is approximately 10 minutes. Regarding the scoring, each question could be given a score of 0 or 1 points. In most items, if the participant’s answer was “yes” or “sometimes”, 1 point would be attributed, meanwhile a negative response would be scored as 0 points. In 3 items, the scoring is reversely made (i.e., “yes” or “sometimes” scores 0 points and “no” scores 1 point). Thereby, the maximum score of this test is 15 points and if the patient has a total score equal or superior to 6 points, there is a possibility that they are frail.

3.3.2. Timed Up and Go (TUG)

TUG measures the time (in seconds) that the patient takes to get up from a chair, walk 3 meters away, turn around, return to the chair, and sit down (Podsiadlo & Richardson, 1991). This test aims to assess mobility, balance, walking abilities and risk of falling in the elderly and usually takes less than 3 minutes. If the patient takes 13 seconds or longer to complete the task, there is a possibility that they are frail. The cut-off score for this test was defined based on specificity and sensitivity exceeding 70% (Savva, Donoghue, Horgan, O'Regan, Cronin & Kenny, 2013; Rodrigues, Teixeira & Forte, 2023).

3.3.3. Cognitive Reserve Index Questionnaire (CRIq)

CRIq provides a standardized measure that accounts for the lifetime cognitive, social, and cultural characteristics of an individual (Nucci et al., 2012). It quantifies three independent CR proxies (CRI- Education, CRI- Work and CRI- Leisure Time) and provides a generalizable CR measure (CRI- Total).

The **CRI-Education** domain records the level of education achieved by the subject. In terms of scoring, 1 point is attributed for each school year completed with success. Training courses outside the sphere of school, lasting at least 6 months, are also taken into consideration, and counted as 0.5 points for every 6 months. Only structured courses with the presence of a teacher are considered.

The **CRI-Work** domain regards the type and duration (in years) of professional activities carried out throughout the subject's lifespan. In this instrument, five work levels are covered, each of which has a different weight in the total score depending on the cognitive complexity it requires and the responsibility it implies, being as follows:

1. Unskilled worker (general services), field work, gardener, service provider support activities at home, driver, call-center operator, babysitter, maid, etc…
2. Craftsman or specialized worker, cook, tailor, counter employee, nursing assistant, military, hairdresser, representative, etc…
3. Trader, specialized employee (non-manual work), religious, commercial agent, musician, real estate agent, kindergarten teacher, etc…
4. Small business manager, qualified independent professional, teacher, entrepreneur, doctor, lawyer, psychologist, engineer, etc…
5. Manager of a large company, leader with high responsibility, politician, university professor, magistrate, surgeon, etc…

In the case of less common jobs or those not covered by the protocol, the cognitive effort and level of responsibility required must be considered. This section only considers paid work that has been carried out regularly during at least 1 year, including activities occurring simultaneously. The classification is assigned secondly by a rounding rule of adding 5 out of 5 years (e.g., a person who was a doctor for 32 years will get a score of 35 and is positioned in the level 4).

The **CRI- Leisure Time** domain records activities that were carried out outside the professional or school hours from the age of 18 onwards. In this section, activities are divided depending on the frequency of performance, according to the perspective of the authors: weekly, monthly, annual, and fixed. For each activity, two possible answers are foreseen: "Never/Rarely" which corresponds to a frequency less than or equal to twice a week/month/year (depending on the nature of the activity) and "Always/Frequently" which corresponds to a frequency equal to or more than 3 times a week/month/year.

The scoring concerns the number of years that an activity was developed in the case of the subject having performed "Frequently/Always", for at least 1 year. The rule of rounding up every 5 years is also followed in this section of the instrument. Fixed frequency activities (number of children or managing the bank account) are considerations independent of temporal stipulations.

It is important to note that, once CRIq has not yet been validated for the Portuguese population, it seemed more appropriate to calculate and analyze the raw scores instead of indices and differences estimates, as performed in the original work by Nucci, Mapelli and Mondini (2012).

3.3.4. Teste de Leitura de Palavras Irregulares (TeLPI)

In **TeLPI** participants are asked to read a list of 30 irregular words, and its score is used as a proxy of premorbid intelligence/CR (Alves et al., 2012). It takes approximately 10 minutes to be completed and the scores were standardized according to years of education.

3.3.5. Montreal Cognitive Assessment (MoCA)

MoCA is a screening test that evaluates executive function, visuospatial capacity, memory, attention, language and orientation (Nasreddine et al., 2005; Freitas et al., 2010). The implementation of this test takes around 20 minutes. The maximum score is 30 points; nonetheless, cut-off scores suggestive of cognitive impairment vary according to the participant's age and years of education (Freitas et al., 2010).

3.3.6. Semantic Fluency Test (SFT)

In **SFT** patients are asked to enumerate the maximum of different animal names as possible in 1 minute (Cavaco et al., 2013). Cut-off scores suggestive of cognitive dysfunction take into consideration the participant's age and years of education (Cavaco et al., 2013).

3.3.7. Geriatric Depression Scale (GDS-15)

GDS-15 is a self-reported depression questionnaire constituted by 15 items that takes approximately 10 minutes to be completed (Sheikh & Yesavage, 1986). A score between 0 and 4 points indicates no clinically significant depressive symptoms, between 5 and 8 points is considered a mild level of depression, between 9 and 11 it indicates a moderate depression level and between 12 and 15 points it is considered a severe level of depression (Sheikh & Yesavage, 1986).

3.4. Data collection

This project was submitted and approved in December of 2022 by the Scientific Council of the Institute of Health Sciences of the Portuguese Catholic University. The project received approval from the Ethics Committee of the institution where data was collected.

The recruitment of participants was done via cellphone, the day before their anesthesiology appointment. During the call, it was explained the content of the study, comprising a cognitive and a frailty assessment in the pre-anesthetic consultation and the fulfillment of questionnaires regarding their physical and psychological health. It was explained that the participation in this study was voluntary and that it took approximately 50 minutes. Exclusion criteria were also screened in this call by questioning about schooling abroad and if there were any history of neuropsychiatric conditions. A script was made to ensure that all information was delivered likewise:

"*The study consists of a cognitive and frailty assessment in the pre-anesthetic consultation. This evaluation is usually carried out on the day of the anesthesiology consultation. We intend to analyze the cognitive domains, such as your memory, your attention and other indicators and ask you to fulfill some questionnaires to find out how you have been feeling physically and psychologically. The main objective of this study is to explore if there are any factors that could bring fragility to the surgery and recovery process. All this lasts approximately 50 minutes.*"

For participants that met the requirements and agreed in participating in this study, the assessment was scheduled for the day of the preanesthetic consultation. In rare exceptions, the preoperative evaluation occurred on the day of the surgery, 3 to 4 hours prior.

Regarding the preoperative evaluation moment, after clarifying any question about the study, the patients were asked to sign an informed consent. Then, demographic variables (such as birth date, education, marital status, height, weight, and clinically relevant history) were collected. Secondly, the assessment of frailty, cognitive reserve, cognitive impairment, and depressive symptoms was performed using the aforementioned instruments. Following this stage, to apply the TUG, the patient was moved out of the room to a specific space where there was a chair and marks on the floor outlining the test area. Data collected from the assessments was stored in a database afterwards.

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) version 28 software, with a pre-defined significance level of $p < 0.05$. Descriptive statistics for sociodemographic and psychometric data included means, standard deviations (SD), minimum, maximum absolute values and percentages. Non-parametric Spearman's Correlation and parametric Pearson Correlations will be performed (for further statistical details, consult appendix 8.1).

In terms of qualitative classifications, correlations were considered "*weak*" when the absolute value of r was < 0.25, "*moderate*" when $0.25 < | r | > 0.5$, "*strong*" when $0.5 < | r | > 0.75$ and "*very strong*" when $| r | > 0.75$ (Marôco, 2021).

4. Results

4.1. Descriptive Statistics

4.1.1. Characterization of the Sample

Initially, the sample was composed by 61 participants that met the eligibility criteria. However, after evaluating the scores from the cognitive and the affective screening instruments, 10 subjects were excluded due to severe cognitive impairment (obtained through MoCA scores, corrected for age and educational level for each participant) and 1 subject was excluded due to severe cognitive impairment and severe depressive symptomatology (reported in the GDS with a score of 12 points).

As presented in Table 1, the final sample is constituted by a total of 50 participants (N = 50), where 26 (52%) were female and 24 (48%) were male. Concerning the ages of the individuals included, the mean age was 71.1 with a standard deviation of 4.5 years. The amplitude of ages varied between 65 and 84 years old, leading to a median of 70.5.

Regarding the variable education (operationalized in years of formal education), the participants presented a mean of 13.1 years of education with a standard deviation of 5.2 years. This variable had a wide amplitude, ranging from 4 to 27 years of education and a median of 14 years (for further information on educational levels, see appendix 8.2.).

Table 1.

Descriptive Statistics of the Sociodemographic Variables (N=50).

	Mean ± SD	*Min*	*Max*	*Median*	*N*	*%*
Sex						
Females	-	-	-	-	26	52%
Males	-	-	-	-	24	48%
Age (years)	71.1 ± 4.5	65	84	70.5	50	100%
Education (years)	13.1 ± 5.2	4	27	14	50	100%

Notes. SD – Standard Deviation; Min – Minimum; Max – Maximum; N – Frequency.

The descriptive statistics of the screening instruments are presented in Table 2. In terms of cognitive functioning, the mean score of MoCA was 25.5 with a standard deviation of 2.7 points. The participants scores ranged from 17 to 30 points, with a median of 26 points. Furthermore, the mean score of SFT was 17.5 with a standard deviation of 4.3 points. The lower score was 7 and the higher was 30, which leads to a median of 18 animals per minute. Lastly, regarding the reported depressive symptoms, the mean score of GDS was 6.4 with a standard deviation of 6 points. The obtained scores varied between 3 and 10 points, leading to a median of 6 points.

Table 2.

Descriptive Statistics of the Screening Instruments.

	Mean ± SD	*Min*	*Max*	*Median*
MoCA	25.5 ± 2.7	17	30	26
SFT	17.5 ± 4.3	7	30	18
GDS	6.4 ± 1.5	3	10	6

Notes. SD – Standard Deviation; Min – Minimum; Max – Maximum.

4.1.2. Characterization of Cognitive Reserve Assessment

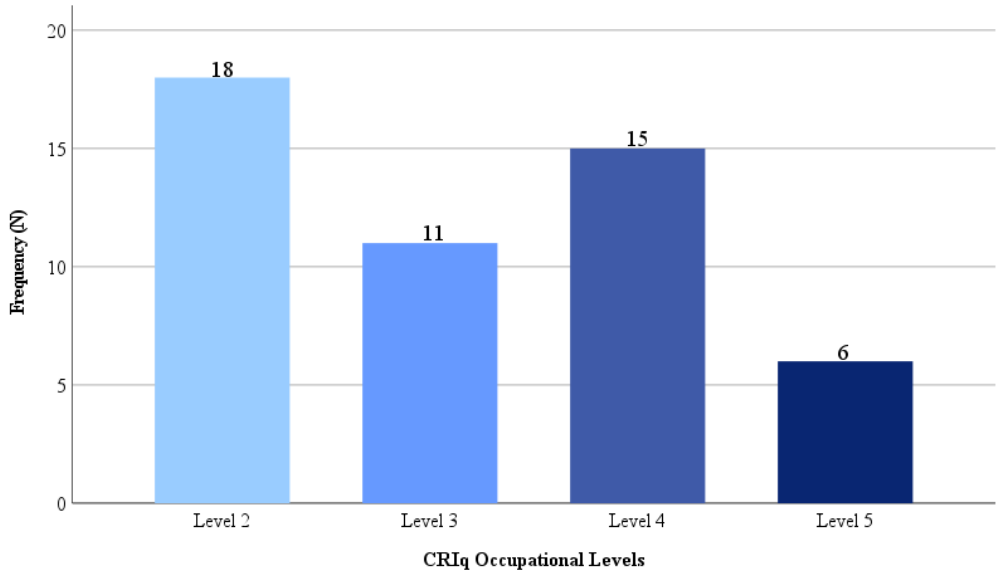
Regarding the CRIq scores, it is important to acknowledge CRI- Education, CRI-Work, CRI- Leisure Time and CRI- Total, as well as the correlations between these measures and sociodemographic variables, such as years of education.

Concerning the **CRI - Education proxy**, this score presented a total mean score of 14.86 years with a standard deviation of 6.25 years (Table 4). The higher frequency years of education were 4 (N = 6), 11 (N = 10) and 16 (N = 13) years. The range varied between 4 and 28 years of education and a median of 14.5.

Regarding the **CRI - Work proxy**, graphic 2 illustrates the frequency of each occupational level. In 23 cases, the participants had various professions during their careers that included more than 1 occupational level. In these cases, the occupational level attributed was the level in which they accumulated more years of experience. For example, if a participant spent 5 years in a profession of level 2 and 30 years in a profession of level 3, they were allocated in level 3.

Figure 2.

Distribution of participants in occupational levels defined in CRI-Work.



Despite the fact that some of the participants exerted professions from level 1 for short periods of time, no participants had a main occupation of level 1. As shown in Table 4, the mean score of CRI- Work was 148.4 points with a standard deviation of 56.36. This domain ranged from 65 to 265 points and presented a median of 140 points.

Respecting the **CRI – Leisure Time proxy**, the activities with higher weekly, monthly, and annual frequency were using new technology (96%), driving (86%) and engaging in domestic activities (86%). On the other hand, the activities with the lowest frequency were volunteering (14%), social activities (18%) and artistic activities (30%). The totality of the sample managed their bank accounts (100%).

Table 3.

Frequency of the activities enrolled from CRI – Leisure Time.

	Total (N=50)
Weekly Frequency	
Reading Newspapers and Weeklies	27 (54%)
Domestic Activities	43 (86%)
Driving	43 (86%)
Leisure Time Activities	27 (54%)
Using New Technology	48 (96%)
Monthly Frequency	
Social Activities	9 (18%)
Cinema or Theater	24 (48%)
Gardening, Bricolage, Sewing, etc.	27 (54%)
Taking Care of Grandchildren/Elderly Parents	37 (74%)
Volunteering	7 (14%)
Artistic Activities	15 (30%)
Annual Frequency	
Exhibitions, concerts, conferences	27 (54%)
Multi-day Trips	34 (68%)
Reading Books	37 (74%)
Fixed Frequency	
Domestic Animals	28 (56%)
Bank Account Management	50 (100%)

Notes. The scores are presented in the following form: Frequency (Percentage).

The mean number of children was 1.78 (SD = 0.89) and there were 4 participants without children. The average score in CRI- Leisure Activities was 355.8 points with a standard deviation of 105.96, a median of 335 and values that varied between 160 and 605 points (Table 4).

In summary, the **raw total scores of CRIq** presented an average of **519.06** (SD = 144.52), with a sparse range of scores varying between 248 and 848 points and a median of 510 points.

Table 4.

Descriptive Statistics of the raw values from CRIq.

	Mean ± SD	*Min*	*Max*	*Median*
CRI - Education	14.86 ± 6.25	4	28	14.5
CRI - Work	148.4 ± 56.34	65	265	140
CRI - Leisure Activities	355.8 ± 105.96	160	605	335
CRI - Total	**519.06 ± 144.52**	248	848	510

Notes. SD – Standard Deviation; Min – Minimum; Max – Maximum

As expected, a strong positive correlation was found between CRI- Total and years of education ($r = 0.57$; $p < 0.001$) (see appendix 8.4., figure 7). Other moderate to very strong correlations were found between education and: CRI- Leisure Time ($r = 0.39$; $p = 0.005$), CRI- Work ($r = 0.64$; $p <0.001$) and CRI- Education ($r = 0.87$; $p <0.001$).

The other instrument used to measure CR, **TeLPI**, had a mean score of 40.60 (SD = 3.13) with raw results varying between 32 and 45 correct answers (Table 5). Concerning the corresponding premorbid IQ, this value ranged between 93.2 (average) and 142.3 (very superior) with a median of 117.6 (high average). Thus, the mean premorbid IQ score was 115.87 (SD = 10.3) which corresponds to a high average IQ level and, subsequently, a high average CR. For more details on the premorbid IQ levels of the sample, see appendix 8.3.

Table 5.

Descriptive Statistics of the derived and raw scores from TeLPI.

	Mean ± SD	*Min*	*Max*	*Median*
Premorbid IQ	115.87 ± 10.30	93.2	142.3	117.6
TeLPI	**40.60 ± 3.13**	32	45	42

Notes. SD – Standard Deviation; Min – Minimum; Max – Maximum

The raw score of TeLPI presented a significant positive correlation with years of education ($r = 0.51$; $p < 0.001$) (see appendix 8.4., figure 8), whereas the premorbid IQ was significantly highly correlated with the educational level ($r = 0.95$; $p < 0.001$).

4.1.3. Correlation between CRIq and TeLPI

Regarding the CR measures, two strong and moderate positive correlations were found between TeLPI raw score and: CRI- Education ($r = 0.54$; $p < 0.001$) and CRI-Work ($r = 0.29$; $p = 0.04$). Premorbid IQ, the derived score of TeLPI, showed moderate to very strong positive correlations with: CRI- Education ($r = 0.87$; $p < 0.001$), CRI- Work ($r = 0.6$; $p < 0.001$), CRI- Leisure Time ($r = 0.3$; $p = 0.03$) and CRI- Total ($r = 0.49$; $p < 0.001$).

Table 6.

Pearson correlation coefficients between CRIq raw scores and TeLPI.

	CRI - Education	CRI - Work	CRI - Leisure Time	CRI - Total
TeLPI	**r = 0.54** (p < 0.001)**	**r = 0.29* (p = 0.04)**	r = - 0.005 (p = 0.98)	r = 0.13 (p = 0.35)
Premorbid IQ	**r = 0.87** (p < 0.001)**	**r = 0.6** (p < 0.001)**	**r = 0.3* (p = 0.03)**	**r = 0.49** (p < 0.001)**

*Notes. * Significant correlation with p < 0.05.*

***Significant correlation with p < 0.01.*

4.1.4. Characterization of Frailty Assessment

On the other hand, TFI scores presented a mean of 3.28 (SD = 2.16), with a lower score of 0 and a maximum of 9 points. The median score of TFI was 3 points, which corresponds to a "non-frail" phenotype. The **TUG**, another measure of frailty, had a mean score of 10.31 (SD = 1.49) with results ranging from 8 to 14 seconds and a median of 10.

Table 7.

Descriptive Statistics for the Tilburg Frailty Indicator (TFI) and the Timed Up and Go (TUG) task.

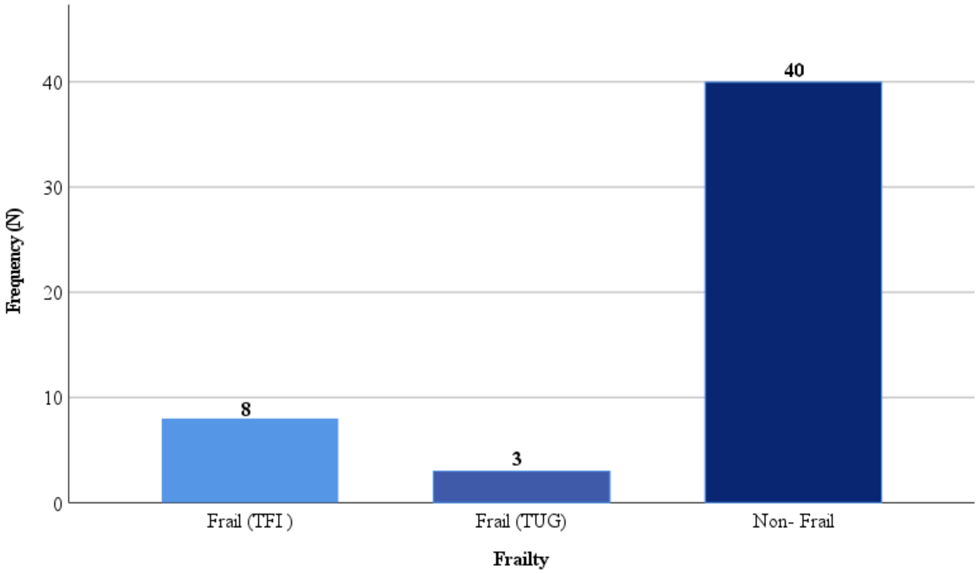
	Mean ± *SD*	*Min*	*Max*	Median
TFI Total	**3.28 ± 2.16**	0	9	3
Physical Components	1.30 ± 1.40	0	5	1
Psychological Components	1.32 ± 1	0	4	1
Social Components	0.66 ± 0.77	0	2	0
TUG (seconds)	**10.31 ± 1.49**	8	14	10

Notes. SD – Standard Deviation; Min – Minimum; Max – Maximum.

In figure 3 it is possible to observe the distribution of the sample according to the presence of frailty based on the selected instruments. According to TFI, only 16% (N = 8) of the sample developed a frail phenotype, as 84% (N= 42) did not meet the criteria for recognition of this condition. On the other hand, TUG reported that 6% (N = 3) of the subjects developed frail and, consequently, 94% (N = 40) did not develop this condition. One subject developed a frail phenotype in both instruments and was considered in both groups. Together, these two instruments indicate that 20% (N = 10) of the participants exhibited frailty.

Figure 3.

Distribution of the sample according to the presence of Frailty.



Notes. The scores were classed according to the cut-offs previously mentioned: Non-Frail (0 – 5 points in TFI and <13 seconds in TUG); Frail (6 – 15 points in TFI or ≥ 13 seconds in TUG).

4.2. Statistical Analysis: Correlations Between Cognitive Reserve and Frailty

4.2.1. Correlation between CRIq and TFI scores

Results from the correlation analysis between the CRIq and the TFI can be found on Table 7. A negative, but not significant, correlation was verified between CRI- Total and TFI- Total ($r_s = -0.18$; $p = 0.21$).

Considering the relation between other CRIq measures and the TFI score, a moderate negative significant correlation was found between CRI- Work and TFI – Total ($r_s = -0.31$; $p = 0.03$); psychological components of the TFI correlated significantly with CRI- Education ($r_s = - 0.3$; $p = 0.03$) and CRI- Work ($r_s = - 0.32$; $p = 0.02$).

The CRIq – Total did not present any significant correlation with Physical ($r_s = -0.16$; $p = 0.27$), Psychological ($r_s = -0.25$; $p = 0.08$) or Social Components of TFI ($r_s = 0.11$; $p = 0.46$). Similarly, TFI - Total was not significantly correlated with CRI- Education ($r_s = -0.24$; $p = 0.99$) or with CRI – Leisure Time ($r_s = -0.08$; $p = 0.96$).

Table 8.

Spearman correlation coefficients between CRIq raw scores and TFI components with respective p-values.

	CRI - Education	CRI - Work	CRI - Leisure Time	CRI - Total
Physical Components	$r_s = - 0.23$ ($p = 0.12$)	$r_s = - 0.28$ ($p = 0.051$)	$r_s = - 0.08$ ($p = 0.6$)	$r_s = - 0.16$ ($p = 0.27$)
Psychological Components	**$r_s = - 0.3$* ($p = 0.03$)**	**$r_s = - 0.32$* ($p = 0.02$)**	$r_s = - 0.16$ ($p = 0.26$)	$r_s = -0.25$ ($p = 0.08$)
Social Components	$r_s = 0.13$ ($p = 0.38$)	$r_s = 0.04$ ($p = 0.78$)	$r_s = 0.15$ ($p = 0.31$)	$r_s = 0.11$ ($p = 0.46$)
TFI - Total	$r_s = - 0.24$ ($p = 0.99$)	**$r_s = - 0.31$* ($p = 0.03$)**	$r_s = - 0.08$ ($p = 0.6$)	$r_s = - 0.18$ ($p = 0.21$)

*Notes. * Significant correlation with $p < 0.05$.*

4.2.2. Correlation between CRIq and TUG scores

Two negative and moderate correlations were found between TUG and: CRI – Total (r = - 0.29; p = 0.04) and CRI – Leisure Time (r = - 0.33; p = 0.02).

Table 9.

Pearson correlation coefficients between CRIq raw scores and TUG raw score with respective p-values.

	CRI - Education	CRI - Work	CRI - Leisure Time	CRI - Total
TUG	r = - 0.003 (p = 0.99)	r = - 0.12 (p = 0.4)	**r = - 0.33*** **(p = 0.02)**	**r = - 0.29*** **(p = 0.04)**

*Notes. * Significant correlation with p < 0.05.*

5. Discussion

The main objectives of the present study were to understand if Cognitive Reserve is associated with Frailty, therefore contributing to the literature regarding this topic and further explore the role that this relation can have in preoperative assessments of elderly patients.

5.1. Correlation between CR and Frailty

Cognitive Reserve is believed to have a protective effect against physiological and age-related changes in the brain (Stern, 2002, 2003, 2009). The ongoing discussion in this topic suggests that CR proxies might also have a protective impact on frailty levels (Sardella et al., 2020). These effects can manifest through a negative relation between CR and frailty, as a high CR might lead to decreased frailty levels.

Four correlations were displayed between years of education and the measures: CRI- Total, TeLPI, Premorbid IQ and TFI- Physical Components. This means that the variable years of education seemed to contribute positively and significantly for the obtained scores in CR measures, as patients with more years of education exhibited higher scores compared to their younger counterparts. It also seemed to have contributed slightly for frailty, once **higher educated individuals reported fewer physical components of frailty**.

Shedding some light into the discovered associations between measures, the moderate and negative correlation found between CRI – Work and TFI- Total seems to suggest that **having a job with higher complexity and responsibility during lifespan reflects on a significant decrease in frailty in advanced ages**. This statistic aligns with the results found in literature, as according to several studies (Stern, 2006; Akbaraly, Portet & Fustinoni, 2009; Garba et al., 2020; Kleineidam et al., 2022) higher cognitive complexity in the work environment seems to improve CR, which in turn might have a significant effect in frailty level in late life.

A recent review attempted to understand how occupation-related variables (e.g., workplace risk factors, job tasks, employment history and organizational job characteristics) influenced the progression of frailty status at advanced age (Iavicoli, Leso & Cesari, 2018). An association was found between life-course occupational conditions and frailty, once low-skilled manual occupations seem to be related to more frailty manifestations (Iavicoli, Leso & Cesari, 2018).

Nevertheless, the limitations of this review may be pointed out, as there seems to be heterogeneity in the definition and assessment tools to evaluate frailty levels across the literature (Collard et al., 2012; Iavicoli, Leso & Cesari, 2018). Additionally, it is not possible to discriminate with certainty if the observed results are related to profession or socioeconomic status, as these variables can be overlapped (e.g., education, income, occupational class) (Iavicoli, Leso & Cesari, 2018). In fact, education plays a crucial role in shaping subjects' knowledge and skills, which subsequently impacts the achievement of more prestigious professions and higher socioeconomic classes. Thus, more research is needed in order to properly define if blue-collar professions independently contribute to the severity of frailty.

In another note, Psychological Components of the TFI demonstrated a negative link with both CRI- Education and CRI- Work, meaning that **subjects with higher educational levels and higher occupational requirements exhibit less psychological problems associated with frailty**. These two moderate correlations seem to indicate that high levels of education (formal and informal) and high occupational attainments throughout life are correlated with the presence of less psychological components of frailty in advanced age. This result is in line with recent research. According to Kondirolli and Sunder (2022), more educated people have less severe psychological symptoms, and each additional year of education lowers the likelihood of reporting symptoms linked to anxiety in 9.8% and depression in 11.3%. Regarding the occupation, several studies linked positive work resources with a lower probability of reporting psychological symptoms (Laditka, Laditka, Arif & Adeyemi, 2023). Hence, the variables education and work activity may act as protective factors for the prevention of appearance of psychological symptoms that can lead to a frail phenotype.

Additionally, a moderate and negative relation between CRI- Leisure Time and TUG was observed. This link appears to indicate that **patients that have more leisure activities execute the TUG faster and, in turn, are less prone to develop frailty**. This finding is consistent with the existing literature, as the beneficial impacts of various leisure activities on health and frailty have been well documented (Scarmeas et al., 2001;

Tucker & Stern, 2011; Garba et al., 2020; Kim, Yi, Kim & Kim, 2020; Sheng, Chen & Qu, 2023). Social leisure activities, such as socializing and building relationships with peers, seem to enhance the quality of social bonds, improve life satisfaction of older subjects and, as a result, diminish the levels of frailty (Kim et al., 2020). Regarding cognitive leisure activities, such as playing cards or using the internet, research has demonstrated that it can slow frailty progression and, in addition, engaging in multiple activities also elicited a more significant effect in frailty levels (Sheng, Chen & Qu, 2023).

Furthermore, it is noteworthy that both the TUG test and the leisure activities incorporated in this study encompass a physical component. This observation may contribute to the correlation between engagement in a higher number of activities, (several of physical nature), and the increased swiftness exhibited by the subjects. This physical component associated with TUG may also explain the discrepancy between frail subjects identified through TFI criteria and TUG criteria. Once TFI offers a more comprehensive understanding of frailty and is a self-report measure, the results may diverge from this distinct measurement assessment.

Having this tendency into consideration, it is essential to promote the engagement in cognitive, social, and physical leisure activities among elderly people (in special, in already frail individuals), as it can stimulate active and healthy aging (Sheng, Chen & Qu, 2023) and decrease the risk of dementia (Scarmeas et al., 2001; Akbaraly et al., 2009).

Ultimately, a very important negative and moderate correlation was found between **CRI- Total and TUG**, which expresses that people that scored higher in CRIq were faster in TUG performance. As these are both composite measures of CR and frailty, respectively, this association can suggest the existence of a correlation between the variables under study and, consequently, **corroborate the main hypothesis of the study**. To the best of our knowledge, this association has not been described before in the literature and can have interesting implications in further preoperative screening assessments.

If this association exists, indeed, it does not seem possible to extract valuable information about CR through TUG, once this frailty instrument has a low variation of results in the population of interest that will not reflect the range of possible results for CR and neither supply complementary indexes (e.g., CRI- Education, CRI- Work and

CRI- Leisure Time). However, this relation can be conversely used in geriatric preoperative screening, as **patients with a higher CR are possibly less prone to develop frailty and, thus, less prone to develop postoperative complications**. This way, applying CR measures in the preoperative moment may be useful to: **1**) Help clinicians decide whether the patient will tolerate the surgical intervention; **2**) Standardize the process of decision (e.g., through cut off scores), reducing the underlying subjectivity; and **3**) Develop a better understanding of the risk-benefit ratio for each particular individual.

In an analytic and final note, the fact that the mean CR level of the sample is very high and that the vast majority of the sample did not develop a frail phenotype is a finding in itself. As referred previously, according to Partridge et al. (2012), the prevalence of frailty in the elderly surgical population is expected to be between 42% and 50%. In this particular sample, the prevalence of frailty is between 6% and 20%. This significant discrepancy of, at least, 22 percentual points can also provide supporting evidence of a negative correlation between CR and frailty and, therefore, reinforce the possible veracity of the main hypothesis of the study.

5.2. Limitations and Implications of this study

It is crucial to underline the primary limitations of this work, several of which are also identified in other research studies concerning CR and Frailty.

Firstly, the utilization of a **non-randomized sampling method** entails evident statistical issues regarding the representation of the population in study and, consequently, the generalization of the results. This type of limitation was not possible to overcome, once the study was performed under a strictly targeted population (i.e., elective surgery patients) with a scarce eligible and available population.

Moreover, it is essential to draw attention to the fact that there can be a bias here. The recruitment and selection process were standardized through a script in order to prevent speech variations and heterogeneity. However, after numerous recruitment sessions, it was clear that the **less frail patients are more available to undertake this kind of study**. Some patients justified the reasons why they would not like to participate, namely: **1**) Patients that were "*too frail*" (according to their words), explained that they would not enjoy exposing their vulnerabilities before undergoing surgery, as it could increase their anxiety, sadness and frailty levels; **2**) Tiredness due to busy scheduling of medical appointments/ongoing treatments; **3**) Comorbidities (such as mobility issues, use of portable oxygen machines or disabling diseases). All of these conditions may have significantly influenced the sample size and the features displayed.

Still regarding the sample scope, it is also valuable to mention that due to the **limited number of frail subjects** within the sample, no significant correlation emerged between the group classified as frail (identified by TFI and TUG criteria) and the non-frail group. Nonetheless, this exploratory analysis did not constitute one of the primary research objectives and, in contrast, the high CR of the subjects enabled the investigation of different questions.

Focusing on the characteristics of the participants, the **atypical educational level** must be addressed. The participants were highly educated if we have into consideration that, in 2022, 64% of the Portuguese population aged 65 or more had between 0 and 4 years of education, 18% had between 5 and 9 years, 7% had between 10 and 12 years and only 11% entered university education (INE, 2023). In comparison, our sample presented 12% of the participants with 0 to 4 years of education, 8% had between 5 and 9 years, 26% had between 10 and 12 years and 54% had more than 12 years of education. As education is one of the main proxies of CR, this tendency was reflected in CR results.

This can be viewed both as a potentiality and a limitation: a potentiality in the sense that it gives important information regarding the features of high CR patients and permits exploration of associations between high CR other measures; and a limitation due to the fact that generalization may not be possible. In light of these considerations, the very high CR level depicted is not representative of a CR level of a randomized sample, which pertains to the issue of **low result reproducibility**. In other words, if the present study was reproduced in a public institution, the results would probably be utterly different.

In terms of protocol challenges, the time needed to complete the study was **considerably extensive**, given the advanced age of the sample and the aggravating factor of being performed in a strikingly vulnerable moment. This concern was raised by some participants and may have led to states of fatigue and diminished motivation. These factors may have potentially interfered with the performance of the individuals.

Lastly, the **lack of consensus** regarding the operational definition of frailty and the use of a spectrum of assessment instruments hampers the process of comparison among studies. Alongside frailty, CR also presents measurement difficulties and heterogeneities across the literature, which can result in less reliable results until consistency is reached.

5.3. Implications on future studies

As referred previously, the **absence of a standardized and unitary method** for assessing CR, coupled with the varied range of tools and criteria used to evaluate frailty, denote methodological challenges that require resolution in future studies (Sardella et al., 2020).

Regarding CR, research lacks assessment of which proxies contribute to this construct, their weighted contribution and the best instruments to assess it (Harrison et al., 2015; Kartschmit et al., 2019). Despite this, CRIq seems to be one of the more complete instruments for CR measurement, with questions covering the current more hypothesized proxies: education, work activity and leisure activities. Thus, in order to utilize CRIq on a bigger scale, more psychometric testing and validation studies across the globe are needed. Regarding frailty, reaching a consensual definition of the construct, a consensual model and a single measure still seems a remote accomplishment. Thereby, the establishment of a standardized and universal measure of these variables for all studies should be a priority of this field of research.

Further steps should consider the **possible relation that was found between CR and Frailty** documented previously, as this association can be operationalized in innovative methods and treatment options. In terms of operationalization and taking into consideration the limitations of the present work, follow-up studies must verify if this relation still exists in a sample with average schooling years and evenly distributed across the educational levels or, in turn, if a low CR sample can be correlated with higher frailty levels. In light of this potential correlation and the previously mentioned constraints, a study involving both a group classified as frail and another classified as non-frail might be relevant to enhance the comprehension of this subject.

Afterwards, with the premise that a condition of frailty can be indicative of postoperative complications to some extent, it can be interesting to study the reliability and validity of the application of CR measures in the preoperative moment, as a **high CR can have an association with less postoperative adverse outcomes**. In order to test this hypothesis, patients undergoing several different types of interventions should be included and adequately separated into clusters to avoid mixed results, as some surgical interventions are linked to higher levels of frailty and higher incidence of postoperative complications than others. The perceived frailty level of the participants can be assessed through self-report questions and should also be taken into consideration with the aim of understanding which surgeries are linked to higher frailty, as it can be an important to analyze the obtained results.

In line with this, other follow-up studies could include the **definition of a cut-off score in CR measures that is linked to diminished level of tolerance to the surgical intervention** or, in other words, a "*too frail for surgery*" phenotype. The aim of this study would not be to prohibit some patients from undergoing surgery, but rather correctly and fully inform them about the underlying risks of that option.

Lastly, in a more preventive point of view, given that frailty can be responsive to interventions that can reduce adverse postoperative outcomes, this can also be tested with **cognitive based interventions**. Maybe, the improvement of cognitive functions via cognitive rehabilitation programs can be associated with decreased levels of frailty in preoperative patients and, thus, better the outcomes of the surgery.

6. Conclusions

The present study presents some evidence of the protective impact that CR seems to have in the frailty level in preoperative patients, as the presence of higher scores in CR proxies (i.e., work activity and leisure activities) seem to be associated with fewer frailty symptoms in various domains (i.e., physical and psychological). In turn, a diminished cognitive reserve could potentially exert an adverse influence on the aging trajectory, once concurrent declines in cognitive and motor/physical functions can ultimately culminate in a frailty phenotype (Sardella et al., 2020).

A lot of implications for geriatric preoperative screening can be drawn from here, as patients with a higher CR are possibly less prone to develop frailty and, thus, less prone to develop postoperative complications. If this is true, assessing CR level in older patients could enable clinicians to consider the potential influence of these factors in frailty status and, ultimately, aiding in the development of a more precise characterization of patients' aging trajectories (Sardella et al., 2020).

Therefore, applying CR measures in the preoperative moment may be useful to help clinicians decide whether the patient will tolerate the surgical intervention, reducing the underlying subjectivity of decision making through the standardization of the process and developing a better understanding of the risk-benefit ratio for each particular individual. This way, both the clinician and the patient can make a fully informed decision of whether or not the hazards overcome the advantages of the intervention.

Given these factors, the forthcoming challenge would involve recognizing CR as a possible contributor among individual reserves, alongside functional and cognitive trajectories that eventually lead to frailty (Sardella et al., 2020).

In a final remark, we consider that this study gave a significant contribution to the CR and frailty research fields. This project can give some support to the application of cognitive reserve instruments before surgery as a reliable prediction of postoperative difficulties (such as Postoperative Delirium, POD, and/or Postoperative Cognitive Dysfunction, POCD). Follow-up studies are essential to investigate the degree of correlation between CR and Frailty and in which ways this relationship can be beneficial for clinical practice.

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8. Appendices

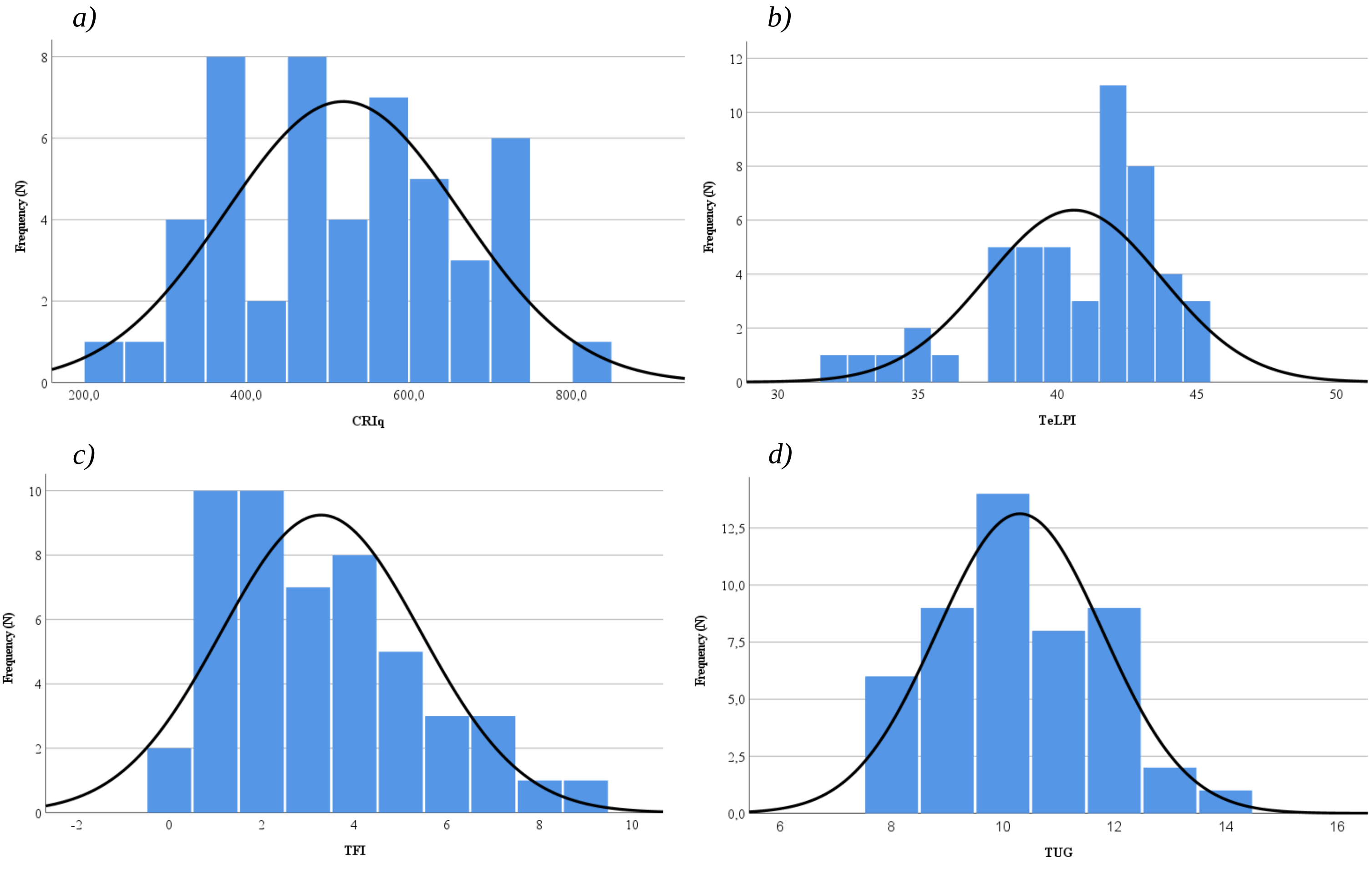
8.1. Statistical Assumptions

In order to utilize Pearson's parametric correlation coefficient, there are 3 assumptions that need to be ensured: 1) Normal distribution of the variables; 2) Linear correlations between variables in test and 3) Absence of outliers.

Regarding the assumption of normality, the Shapiro-Wilk tests demonstrated that TeLPI ($p = 0.003$), TFI ($p = 0.01$) and TUG ($p = 0.02$) did not have a normal distribution in opposition to CRIq ($p = 0.37$). However, evoking the **Central Limit Theorem**, we can consider that all of the variables in study have a normal distribution due to the reasonable size of the sample (i.e., > 30) (Marôco, 2021).

Figure 4.

Distribution of the variables in histograms.



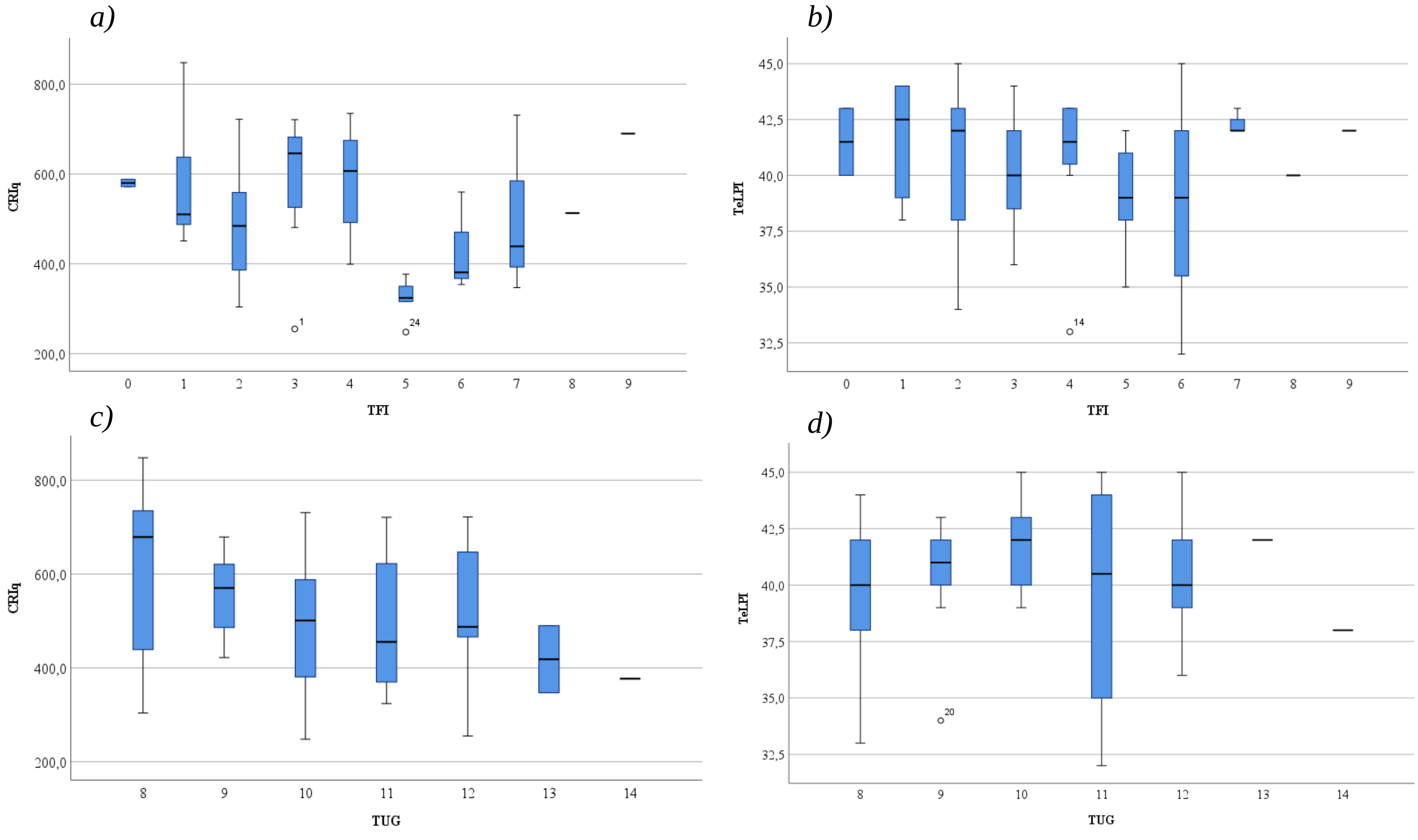
Notes. Legend: a) CRIq scores distribution; b) TeLPI scores distribution; c) TFI scores distribution and d) TUG scores distribution.

In this matter, parametric tests are robust to violation of the assumption of normality if the value of Skewness is inferior to 3 and the value of Kurtosis is inferior to 7 (Marôco, 2021). CRIq scores demonstrated symmetric scores around the mean (Sk = 0.08) and a platykurtic distribution (K = -0.79). TeLPI scores exhibited symmetric scores around the average (Sk = -0.95) and a leptokurtic distribution (K = 0.5). In contrast, TFI scores presented asymmetry to the right (Sk = 0.69) and a platykurtic distribution (K = -0.13). Finally, TUG scores also presented asymmetry to the right (Sk = 0.28) and a platykurtic distribution (K = -0.490). Therefore, all of the variables fulfill this condition and it is possible to affirm there is a **normal distribution**.

Despite the fact that all of the relations are relatively linear, the presence of outliers in graphs a), b) and d) does not confer sufficient criteria for parametric testing (Marôco, 2021). Therefore, non-parametric Spearman's Correlations were performed in these cases and parametric Pearson Correlations was performed in case c) (i.e., correlation between CRIq and TUG).

Figure 4.

Box-Plots of CR and Frailty measures.

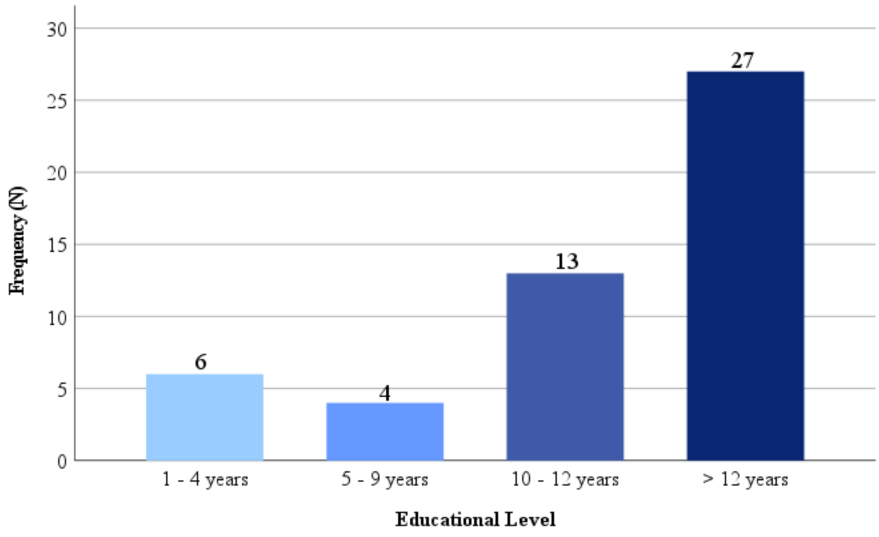


Notes. Legend: a) Relation between CRIq and TFI; b) Relation between TeLPI and TFI; c) Relation between CRIq and TUG and d) Relation between TeLPI and TUG (N = 50).

8.2. Educational Levels

Figure 5.

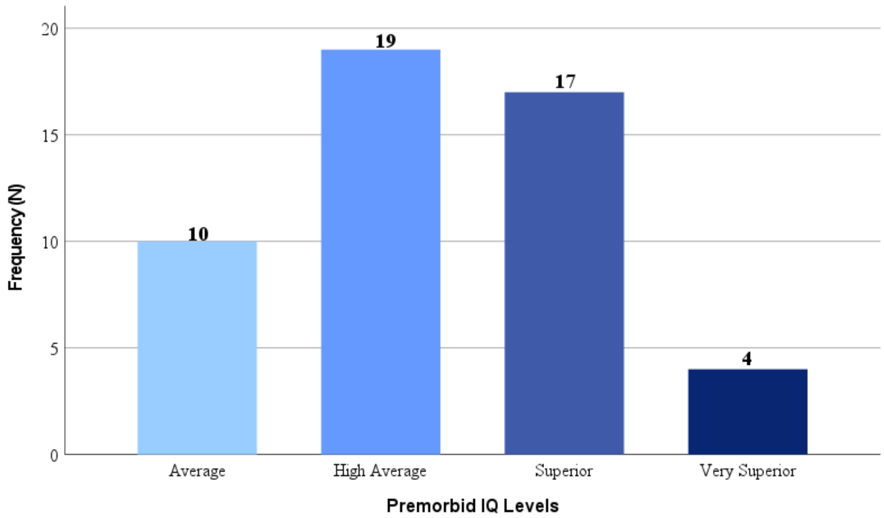
Distribution of the participants in educational levels.



8.3. Premorbid IQ Levels

Figure 6.

Distribution of the sample in IQ Levels derived from TeLPI scores.



Notes. The scores were grouped according to Weschler IQ classification in WAIS-IV, namely: Average (90 – 109); High Average (110 – 119); Superior (120 – 129); Very Superior (>130).

8.4. Correlations between Years of Education and: CRI-Total and TeLPI

Figure 7.

Relation between CRI- Total and years of education.

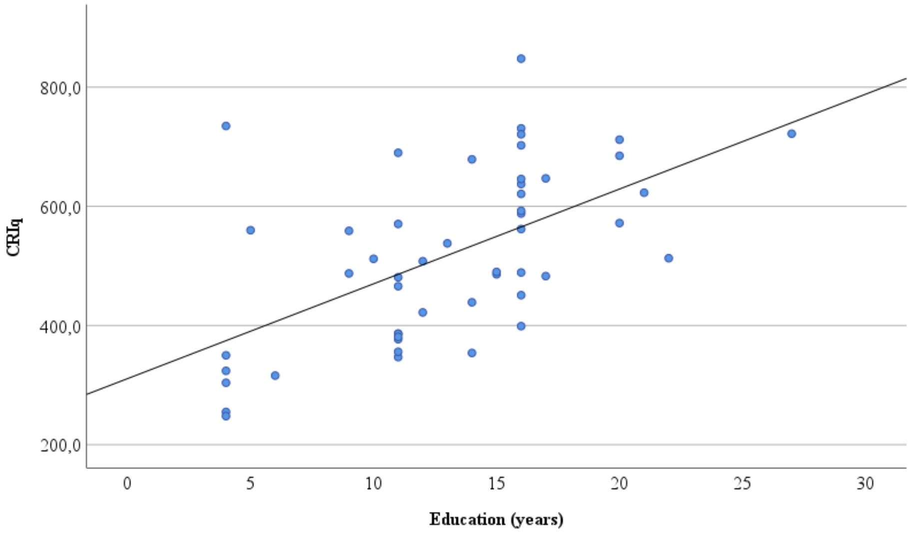


Figure 8.

Relation between TeLPI and years of education.