Review article

Potential Blood-based Biomarkers for Cognitive Frailty: A Narrative Review

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Abstract

Cognitive frailty (CF), which refers to the coexistence of physical frailty and cognitive impairment, is predicted to rise as the global aged population continues to grow. As such, reliable biomarkers are needed to facilitate diagnosis. It is hypothesised that blood-based biomarkers, which are non-invasive, simple and inexpensive, may be useful for diagnosis of CF. The current narrative review was undertaken to perform a literature search of journals on blood-based biomarkers for CF published between 2016-2021 and to critically review the relevant journals. The literature search for published journals was performed using ScienceDirect and PubMed, and was facilitated by a combination of keywords which included blood biomarkers and CF. Further to the processes of screening and checking of published literature for eligibility based on inclusion and exclusion criteria, 19 articles were shortlisted and critically reviewed. Basically, tryptophan, C-reactive protein (CRP), total cholesterol and vitamin D were found to be the major blood-based biomarkers for CF as they were all reported by at least 2 studies. On average, tryptophan levels in CF group were 1.4 times lower than control. The majority of the blood-based biomarkers of CF were involved in amino acid (AA) metabolism and inflammatory response pathways. In general, blood-based biomarkers (i.e., tryptophan, CRP, total cholesterol and vitamin D) may be useful for diagnosis of CF but require further studies.

Keywords: Cognitive frailty, ageing, blood, biomarkers, diagnosis

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Received 12 Jan 2023; accepted 01 April 2023
Available online: 15 June 2023 http://doi.org/10.24191/IJPNaCS.v6i1.02

1.0 Introduction

Cognitive frailty (CF) is common amongst the older adults (1). The elderly population worldwide is growing and is expected to reach 1.5 billion in 2050, which is more than double the number of elderly people in 2019 (2). With the projected global growth of elderly people, it is likely that the prevalence of CF may increase as well. At present, the global prevalence rate of CF is reported to be between 1.0 to 9.8% (1, 3, 4). Likewise, the ageing population in Malaysia is also on the rise and the country is forecasted to be an ageing nation by 2030 (5). A cohort study amongst 815 multi-ethnic elderly people reported that the prevalence rate for CF and cognitively pre-fail groups were 2.2% and 37.4%, respectively (3).

Basically, CF is a term that emerged from accumulating evidence on the interrelationship between frailty and cognitive impairment (6). It refers to a heterogeneous clinical manifestation characterised by the simultaneous experience of physical frailty and cognitive impairment but in the absence of dementia (7). It is also linked to increased risk of dementia and neurodegenerative disorders amongst older adults (8, 9). In fact, CF is the leading cause of falls, hospitalisation, disability or dependence in daily activities and death (1, 10). Given that it is often being described as reversible (4, 11), CF is also subdivided into potentially reversible and reversible CF (12), whereby the former is indicated by mild cognitive impairment (MCI) and positive biomarkers whilst the latter is by pre-MCI subjective cognitive decline (SCD) (12). The physical aspects of both subtypes are the same which are frailty and pre-frailty (13).

At present, the physical frailty aspect of CF can be diagnosed by a number of simple rapid screening tests (14), which include the Fatigue, Resistance, Ambulation, Illness and Loss of Weight (FRAIL) Questionnaire. There are also a number of available tests that are deemed to be sensitive in discriminating healthy people from those with cognitive impairment. These tests include the Mini Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), General Practitioners Assessment of Cognition (GPCog), Clock Drawing Test (CDT) and Verbal fluency, just to name a few (15-18). However, the Alzheimer's Association Medicare Annual Wellness Visit Algorithm for Assessment of Cognition reviewed and reported that these cognitive tests are associated with several biases. These tests lack quantity and quality in published research and appropriate validation in population with different educational levels. Moreover, only limited number of studies had compared the use of these tests in population-based screening with more targeted approaches (18). It therefore remains unclear as to which tests and which combination of tests could accurately distinguish CF in clinical settings (19). There are also discrepancies in predicting cognitive-related outcomes due to the different subtypes of CF (20, 21). Not to mention, the lack of validity and reliability of operationalisation of the two components of CF (22).

The need to improve the diagnostic standard and accuracy of CF has led to the search for potential biomarkers. Biomarkers will be able to greatly improve screening for CF as physical frailty and cognitive impairment share the common ageing biomarkers (13). In this regard, potential blood-based biomarkers for CF have received attention (23-25). Blood-based biomarkers are more time- and cost-effective as the procedures are repeatable, non-invasive, simple and inexpensive (26). They are also more

suited to be used for monitoring long term treatment outcomes and large-scale screening (27). For this purpose, the present review highlights the potential of blood-based biomarkers in diagnosing CF.

2.0 CF

2.1 Reversible CF

Reversible CF include the cognitive impairment aspect of subjective cognitive decline (SCD). The term SCD refers to individuals who exhibit normal performance in cognitive testing even though they have altered subjective cognitive function whether in terms of memory dysfunction or deterioration of executive function, language, attention and visuospatial function but typically more towards the memory domain (20, 28). It is suggested that SCD may serve as a potential target for early intervention of neurocognitive disorders (29). SCD is incorporated into the 2018 National Institute on Aging–Alzheimer's Association (NIA-AA) research criteria for AD whereby it is characterised by a transition phase between normal cognition and early stages of neurocognitive disorders (30). Therefore, it is suitable to serve as a secondary target for prevention of cognitive impairment and as a diagnostic criterion for CF.

2.2 Potentially reversible CF

Potentially reversible CF is referred to as MCI (31). Patients with MCI is reported to struggle in performing daily activities as opposed to SCD (32). The MCI stage is considered to be an advanced form of SCD. It is reported that during the MCI stage, the cognitive damage is irreversible as neuronal loss exceeds physiological ability of the brain to compensate (20). Nevertheless, there are cases whereby MCI patients experience symptoms that are reversible and are able to regain normal cognitive function (33). Hence, this subtype is potentially reversible.

2.3 Pathogenesis of CF

The mechanisms that link cognitive impairment and physical frailty appear to be multifactorial (22) and the common consequences of ageing may affect these age-related conditions (20). The ageing mechanisms involve cell senescence, alterations in intercellular signals, disorders of the regulatory systems, neuroendocrine dysfunction, inflammation and immune senescence (20, 34, 35), all of which increase the state of vulnerability and gradually decrease the physiological reserves of multiple organs. Moreover, the presence of abnormalities, particularly pathophysiological modifications, may accelerate the depletion of the physiological reserves, causing homeostatic failure, physical frailty, or CF (20, 36). The pathophysiological modifications include cardiovascular elements like diabetes, dyslipidemia, hypertension, and inflammation, nutritional factors like vitamin D deficiency, hormonal factors like reduced testosterone, insulin resistance, lifestyle and mental health issues. These factors that cause cognitive impairment are associated with the development and worsening of physical frailty (37).

2.3.1. Vascular risk factors

Vascular damage due to atherosclerotic vascular diseases or embolic events would result in reduced blood flow to tissues located in the brain, skeletal muscles or heart. Vascular diseases may result in cognitive decline amongst the elderly population as cognitive deterioration would occur following a reduction in blood flow (38, 39). The decreased blood

flow could lead to impaired function of skeletal muscles, predisposing to frailty. Vascular problems are reported to be a key etiological factor in geriatric syndromes which include frailty (40, 41). In fact, frail older adults are observed to have an upgraded platelet activity when compared to healthy controls (42), which could increase the risk for thrombosis.

2.3.2. Hormonal factors

Several hormones which link both frailty and cognitive decline to the hormonal changes could affect skeletal muscle decline and cognition (43, 44). Low testosterone levels are observed amongst older men and this results in loss of muscle mass and strength which predisposes to sarcopenia (45). Similarly, low testosterone levels are hypothesised to be associated with cognitive function and MCI (46). Testosterones influence the synaptic plasticity in the hippocampus and modulate the accumulation of amyloid beta protein (47, 48). Levels of growth hormone (GH) is also reduced with increased age. Levels of insulin-like growth factor I (IGF-I) and dehydroepiandrosterone sulfate (DHEA-S) were found to be significantly lower in frail individuals when compared to non-frail individuals. Furthermore, interleukin 6 (IL-6), which is inversely associated with low levels of IGF-I, was found to be at high levels amongst the frail group (49). As for cognition, GH induces cognitive behaviors such as learning and memory and influences synaptic plasticity (50). Some other hormones like cortisol (51) and ghrelin (52) have also been reported to affect frailty and cognition.

2.3.3. Vitamin D

Reduced level of vitamin D is seen amongst the elderly and is associated with deterioration of physical performance and higher probability of falls, fractures, frailty and death (53, 54). Also, it has a significant effect on the development of sarcopenia as it is positively correlated with muscle mass and muscle strength and may possibly improve physical functioning and decrease incidents of falls amongst patients supplemented with vitamin D (39). Moreover, epidemiological studies demonstrated that low level of vitamin D is strongly correlated with prevalence and incidence of frailty (39, 55). In terms of cognition, lower vitamin D intake is associated with significantly worse outcome in one or more cognitive function tests or a higher risk for dementia (56). A cross-sectional study even suggested that serum 25-hydroxyvitamin D may be linked to executive functioning and information-processing speed among frail and prefrail subjects (57).

2.3.4. Inflammation

Inflammation is a process that involves multiple cytokines and other inflammatory proteins. Serum IL-6 and CRP were associated with low Modified MMSE (3MS) scores and cognitive decline among well-functioning elders (58). Increased serum interleukin-8 (IL-8) is linked to poor performance in memory and speed domains and in motor function (39). Previous cohort studies indicated that IL-6 and tumour necrosis factor alpha (TNF- α) as markers of frailty (59, 60). The inflammatory process was also reported to influence the progress of both frailty and cognitive impairment (61).

2.3.5. Insulin resistance

Insulin resistance leads to hyperinsulinaemia. Hyperinsulinaemia, which predisposes cells to high levels of insulin for a long period of time, would adversely affect the function and survival

of the cells including neurons. High concentration of glucose could damage the neurons and result in cognitive impairment. When comparing scores for MMSE, MOCA, CDR, orientation, delayed memory and attention/ calculation domains, participants with hyperinsulinaemia demonstrated worse cognitive functions when compared to those without hyperinsulinaemia (62). Frailty was found to be significantly associated with insulin resistance and C-reactive protein levels (63). Pérez-Tasigchana et al. (64) demonstrated that diabetes and insulin resistance increased the risk of frailty and low grip strength had the strongest association with diabetes.

2.3.6. Nutrition

The risk of incident cognitive decline and dementia are influenced by vitamins, micro and macro-nutrients, lipids and antioxidants (65). Malnutrition is a common problem in the elderly and it has been linked to MCI. Lee et al. (66) showed that most of the participants who had low MMSE scores, were in the moderate or high nutritional risk state. Furthermore, MCI was also associated with diets that are high in processed foods (67). Malnutrition is also linked to frailty whereby a significant correlation was found between protein intake and frailty. It was suggested that a 20% increase in protein intake may be associated with 32% decrease of frailty (39).

3.0 Current diagnostic tools

3.1 Diagnostic tools for physical frailty

Table 1 lists the common diagnostic tools for physical frailty. The CHS or Freid's phenotypic model is often used as a reference to diagnose frailty (68). Basically, physical frailty or frailty is operationalised by a condition of three or more of the following five phenotypic criteria; weakness (i.e., low grip strength), slowness (i.e., slowed walking speed), low level of physical activity, self-reported exhaustion and unintentional weight lost. If one or two of the criteria are fulfilled, it is considered as a pre-frail stage, a risk factor for frailty progression (69).

The Clinical Frailty Scale (CFS), on the other hand, is a face-to-face assessment used to evaluate any underlying diseases, degree of exercise and basic daily living activities (70). The scores are divided into categories 1 to 9, whereby category 1 is considered as fit and category 9 as terminally ill. Other tool like the simple FRAIL questionnaire consists of only five short yes or no questions with a maximum score of 5 (71). The questions covered on fatigue of the individual, ability to walk up the stairs, distance of walking, underlying diseases and weight loss. Gerontopole Frailty Screening Tool (GFST) (72) and Program of Research to Integrate Services for the Maintenance of Autonomy (PRISMA-7) questionnaire (73) are also of similar structure. GFST questions cover the same areas as FRAIL but with the addition of memory problems and enquiring if individuals live alone. As for PRISMA-7, it touches areas on age, health problems and old-age dependency.

Table 1: List of the diagnostic tools for physical frailty.

Diagnostic tools	Reference
Cardiovascular Health Study (CHS) or Fried's definition	(68)
The Clinical Frailty Scale (CFS)	(74)
Gerontopole Frailty Screening Tool (GFST)	(75)
FRAIL (Fatigue, Resistance, Ambulation, Illnesses, Loss of weight) questionnaire	(117)

Program of Research to Integrate Services for the Maintenance of Autonomy (PRISMA-7)	(77)

3.2 Diagnostic tools for cognitive impairment

Table 2 lists the common diagnostic tools for cognitive impairment. The CDR, which is a global rating tool for cognitive impairment by a clinician first introduced in 1982, consists of two different sets of questions, one is designed for the caregiver (informant) and the other for the subject. The scores are in the range of 0 to 3 with higher scores indicating a more severe cognitive impairment; no dementia (CDR=0), questionable dementia (CDR=0.5), MCI (CDR=1), moderate cognitive impairment (CDR=2), and severe cognitive impairment (CDR=3). Basically, CDR evaluates six different cognitive and behavioural domains which include memory, orientation, judgment and problem solving, community affairs, home and hobbies performance, and personal care (78).

The MMSE, on the other hand, is widely used for diagnosis of MCI and dementia in research and clinical settings. It consists of eleven questions divided into two sections. Whilst the first part covers orientation, memory, and attention, the second part assesses the ability to name, follow verbal and written commands (79). The scores are in the range of 0 to 30 and total scores of below 23 is suggested to be cognitively impaired (80).

MoCA, the relatively newer diagnostic tool, is a one page 30-point test whereby it evaluates memory, visuospatial abilities, executive functions, attention, concentration language and orientation to time and place (81). The scoring system for this test is as follows; mild cognitive impairment (scores of 18–26), moderate cognitive impairment (scores of 10–17) and severe impairment (scores less than 10) (80).

Table 2: List of common diagnostic tools for cognitive impairment.

Diagnostic tools	Reference
Clinical Dementia Rating (CDR)	(82)
Mini-Mental State Examination (MMSE)	(83)
Montreal Cognitive Assessment (MoCA)	(81)

3.3 Diagnostic tools for CF

Based on the definition of CF by the International Consensus Group (84), physical frailty is operationalised by the CHS phenotypic model (22). As such, the use of CHS can be seen in most CF-related studies despite the many different frailty diagnostic tools (3, 4, 11, 85-87). The cognitive impairment aspect of CF, on the other hand, corresponds to the concept of CDR score of 0.5 whilst the exclusion of concurrent dementia correspond to the concept of MCI (84). Unfortunately, a CDR score of 0.5 is reported to be inaccurate for the diagnosis of MCI as previous study reported that 39.7% of people with a CDR score of 0.5 were found to be demented (88, 89). Furthermore, CDR is difficult to be implemented into busy clinical settings as it requires a clinician to obtain information from the patient and caregiver, and rate the cognitive performance of the patient in several domains (88). The use of CDR is also rarely seen within studies on cognitive frailty (3, 4, 11, 85-87) and instead the use of MMSE is predominant.

In spite of the fact that it is commonly used, MMSE has many shortcomings such as the lack of standard administration procedure, the inability to administer to illiterate subjects due to the requirement of reading and writing component, significant educational bias and low

diagnostic criteria for dementia (90). It is also difficult to implement this tool in primary care settings as it requires time and special training for administration and scoring. In MoCA, the memory testing involves more words, fewer learning trials, a longer delay before recall and presented with more numerous and demanding tasks overall (81).

Nevertheless, no consensus was reached on which diagnostic tools for cognitive impairment is most accurate for use in detecting CF (19, 91). Furthermore, the Alzheimer's Association Medicare Annual Wellness Visit Algorithm for Assessment of Cognition reviewed that there are limited number of studies that investigate the comparison between the use of MMSE and MoCA in population-based screening and more targeted screening (92). Not to mention the poor validation of the existing diagnostic tools that can potentially lead to over-diagnosis (18). For example, it was reported that as many as 1 in 8 healthy individuals screened for dementia and MCI are incorrectly classified using the MMSE while 1 in 4 are screened incorrectly using the MoCA (93).

3.4 Potential blood-derived biomarkers for CF

Blood-derived biomarkers offer several advantages over CSF-derived biomarkers. Generally, blood-derived biomarkers are more acceptable by patients, cost and time effective as well as practical at the population level (94). Table 3 summarises the blood-based biomarkers for CF based on literature. However, the major blood-based CF biomarkers that have been replicated in more than one study (Table 4) are tryptophan (Trp) (95, 96), C-reactive protein (CRP) (96, 97), total cholesterol (TC) (98, 99) and vitamin D (25, 100). Major blood-based CF biomarkers

Trp, one of the major blood-based CF biomarkers, was found to be downregulated in CF group when compared to the control group. A cross-sectional study reported the mean concentration of Trp as 0.8 times lower in frail group and 1.2 times lower in cognitive impaired group when compared to control group (95). Similarly, another cross-sectional study reported that the concentration of Trp in CF group (51.31nmol/L) was 1.2 times lower than that of control group (59.41 nmol/L) (96). Trp is an essential amino acid crucial for protein synthesis. It also functions as substrate for the synthesis of several bioactive compounds with important physiological roles. Basically, humans lack the biochemical pathways to synthesise Trp. It is acquired from diet at a daily dose of 3.5 mg per kg of weight (101). The best-known function of Trp is probably its conversion to monoaminergic neurotransmitter serotonin (5-hydroxytryptamine, 5-HT). 5-HT, an important neurotransmitter that controls adaptive responses in the central nervous system (CNS), is linked to alterations in mood, anxiety or cognition (102). Besides, the product of Trp degradation, kynurenine, is associated with muscle related problems. Kynurenine was found to induce both muscle and bone loss in mice (103). Elevated levels of kynurenine were also seen in patients with fragile hip fractures (104). Notably, inhibition of Trp degradation and indoleamine 2,3-dioxygenase (IDO) activity using the experimental tryptophan mimetic, 1-methyl-D-tryptophan (D-1MT), could enhance muscle function in aged mice (103). This suggests that regulating kynurenine accumulation with ageing might be a potential pathway for improving musculoskeletal function (105).

With regards to total cholesterol (TC), another major blood-based CF

biomarker, its mean concentration was found to be 1.0 times lower in the CF group (5.3 μmol/L) than control group (5.5 μmol/L) in the male participants (98). However, the baseline levels were the same amongst the female participants in both CF and control groups (5.9 mmol/L). The study also found the high-density lipoprotein cholesterol (HDL) levels to be lower in the CF group but higher in control group. Amongst the male participants, the baseline levels of HDL were 1.03 times lower in CF group (1.17 mmol/L) than in control group (1.21 mmol/L) whereas amongst the female participants, the baseline levels were 1.1 times lower in CF group (1.39 mmol/L) than in control group (1.51 mmol/L). Interestingly, the same study observed that along the 5-year period follow-up, the cholesterol levels increased prior to becoming cognitively frail but decreased after becoming so (99). The mean concentration of cholesterol, which was around 6.3 mmol/L, increased up to 6.4 mmol/L prior to cognitive frailty incident. The mean concentration then declined until 6.2 mmol/L. As for control group, the cholesterol levels increased steadily overtime. This was only observed amongst the female participants.

TC, low density lipoprotein cholesterol (LDLc) and triglycerides (TG) would increase with age (106). Additionally, lipoprotein kinetics studies demonstrated that the fractional clearance rates of very low-density lipoprotein cholesterol (VLDLc), intermediate density lipoprotein cholesterol (IDLc) and LDLc-Apo B decrease with age (107, 108). That said, frailty which is also age-related, has been found to be associated with the lowering of TC, LDL and non-HDL cholesterol (non-HDLc) (109). Low cholesterol was found to precede the development of frailty phenotype (110). The relationship of TC and cognition is generally inconsistent. A study found that higher TC and/ or higher LDL were associated with poorer cognitive performance (111) or a higher risk of AD (112). Other studies, however, reported otherwise. It was found that higher TC and/ or higher LDL levels were associated with better cognitive performance (113) or lower risk of dementia/ cognitive decline (114). Moreover, it was suggested that HDL was positively correlated with cognitive functions (115). Amongst community-dwelling older people, individuals affected by dementia were presented with significantly lower TC, non-HDL and HDL levels (116).

Vitamin D, yet another major blood-based CF biomarker, was found to be the lowest in CF group (21.14 ng/mL) when compared to CI (23.91 ng/mL), physical frail (23.39 ng/mL) and control groups (25.69 ng/mL) (25). Additionally, a study which recruited only female participants reported the levels of vitamin D to be 0.6 times lower in frail/ prefrail group than control group (100). The mean concentration was 29 ng/mL in prefrail women and 28 ng/mL in frail women but 46 ng/mL in controls. Insufficient vitamin D was linked to cognitive decline or dementia. Vitamin D has been postulated to be involved in a range of neuroprotective mechanisms which included increased phagocytosis of amyloid-beta peptide, regulation of neurotrophins and calcium homeostasis, anti-inflammatory and antioxidant actions that prevent dementia (117, 118). Vitamin D receptors, which are expressed in the nucleus of muscle cells (119), have been shown to influence muscle cell contractility (120). The receptors may modulate muscle strength by increasing the *de novo* synthesis of protein (121). Besides, vitamin D receptors in muscle tissues decrease with age which may in turn increase the risk of diminished muscle strength in later life (122).

CRP, on the contrary, was upregulated in CF group when compared to control group. The plasma CRP level in CF group was found to be 1.7 times higher than that

Table 3: Blood-based biomarkers for CF.

Country	Study Design / Mean age	Number of subjects				Follow up period/ Duration	Blood fraction	Platform	Biomarkers	Main findings	References
		Controls	Frailty/ PF	CI	CF						
Malaysia	Cross-sectional study Mean age: 67.63 (controls) 69.44 (CF)	M: 234 F: 265	NA	NA	M: 138 F: 187	-	Serum & Plasma	-	Oxidative stress markers & Genetic markers	Malonaldehyde: 1.4 times higher in CF group (2.71 nmol/L) compare to controls (1.97 nmol/L). Telomerase: 1.2 times lower in CF group (5.76 nmol/L) compare to controls (7.16 nmol/L). <u>Conclusion</u> Malonaldehyde levels ↑ while telomerase levels ↓ in CF group compare to controls.	(3)
Germany	Cross-sectional study Mean age: 53.4 (controls) 62.8 (PF) 64.3 (CF)	1628 *Did not specify gender	NA	NA	199	-	Plasma, serum & peripheral blood mononuclear cells (PBMC)	-	Antioxidant & metabolomic markers	β-cryptoxanthin: 0.7 times lower in CF (0.15 μmol/L) group compare to non-frail group (0.22 μmol/L) Zeaxanthin: 0.8 times lower in CF group (0.036 μmol/L) compare to non-frail group (0.044 μmol/L). Cholesterol: 0.9 times lower in CF group (5.3 μmol/L) compare to non-frail group (5.5 μmol/L) α-tocopherol: 0.9 times lower in CF group (26.6 μmol/L) compare to non-frail group (27.8 μmol/L).	(99)

										Guanidinoacetate: 0.9 times lower in CF group (7.6 μmol/L) compare to non-frail group (8.4 μmol/L). <u>Conclusion</u> β-cryptoxanthin, Zeaxanthin, Cholesterol, α-tocopherol, and guanidinoacetate levels ↓ in CF group compare to controls.	
Netherlands	Longitudinal study Mean age Controls: 63.0 (males) 64.6 (females) CF: 65.5 (males) 66.9 (females)	M: 606 F: 304	NA	NA	M: 303 F: 152	5 years	Plasma	Roche/Hitachi Modular P analyzer	Cardio-metabolic, inflammatory, & oxidative stress markers	Total Cholesterol (TC): In men, the baseline levels are 1.03 times lower in CF group (5.3 mmol/L) than in controls (5.5 mmol/L). In women, the baseline levels are the same in CF group (5.9 mmol/L) and in controls (5.9 mmol/L). *Increased before became cognitively frail and decreased after incident cognitive frailty. (Values in graph) HDL Cholesterol: In men, the baseline levels 1.03 times lower in CF group (1.17 mmol/L) than in controls (1.21 mmol/L). In women, the baseline levels 1.1 times lower in CF group (1.39 mmol/L) than in controls (1.51 mmol/L). GGT: In men, CF (27 U/L) than controls (28 U/L)	(98)

										In women, no differences between CF (19 U/L) and controls (19 U/L) Urea: In men, no differences between baseline level CF (6.2mmol/L) and control group (6.2 mmol/L). In women, 1.1 times higher in CF group (6.1 mmol/L) than controls (5.8 mmol/L). <u>Conclusion</u> Overtime, total cholesterol ↓, urea ↑ while GGT remains stable in those that became cognitively frail.	
Japan	Cross-sectional study Mean age: 88.2 (frail) 80.5 (non-frail) 85.5 (CI) 79.0 (no CI)	10 (non-frail) 4 (no CI) *M: 7 *F: 12	9	15	NA	-	Whole blood	LC/MS	Metabolomic markers	*Real values based on Peak area <u>Frailty</u> Acetyl-carnosine: 0.5 times lower in frail group (1.5) compare to non-frail group (3.1) ET: 0.5 times lower in frail group (396.66) compare to non-frail group (752.39). Tryptophan: 0.8 times lower in frail group (170.77) compare to non-frail group (214.57). Creatine: 1.4 times higher in frail group (31.83) compare to non-frail group (22.26).	(95)

										UDP-glucuronate: 1.6 times higher in frail group (1.60) compare to non-frail group (1.02). <u>Cognitive impairment</u> Acetyl-carnosine: 0.5 times lower in CI group (1.5) compare to non-CI group (3.1). ET: 0.6 times lower in CI group (502.05) compare to non-CI group (890.78). Tryptophan: 1.2 times lower in CI group (185.75) compare to non-CI group (224.10). Creatine: 1.8 times higher in CI group (29.60) compare to non-CI group (16.27). UDP-glucuronate: 1.5 times higher in CI group (1.40) compare to non-CI group (0.91). <u>Conclusion</u> (Acetyl-carnosine, ET, and tryptophan) levels ↓ while creatine and UDP-glucuronate levels ↑ in those frail and CI group.	
France	Cross-sectional study Mean age: 74.27	M: 170 F: 384	M: 106 F: 281	M: 137 F: 189	M: 162 F: 201	-	Plasma	Electro-chemi-luminescence competitive binding assay &	Nutritional markers	Lowest mean concentration of vitamin D in CF group (21.14 ng/ml) compare to CI group (23.91 ng/mL), frail	(25)

	(controls) 76.04 (PF), 74.79 (CI), 77.03 (CF)							enzymatic cycling assay		group (23.39 ng/mL) and controls (25.69 ng/mL). Highest level of mean concentration of tHcy in CF group (16.83 µmol/L) compare to CI group (15.25 µmol/L), frail group (16.07 µmol/L), and controls (15.61 µmol/L). <u>Conclusion</u> Vitamin D levels ↓ while tHcy levels ↑ in CF group compare to other groups.	
Brazil	Cross-sectional study Mean age: 69.57 (controls), 72.25 (PF), 71.64 (CI), 74.84 (PF + CI)	M: 10 F: 13	M: 1 F: 7	M: 3 F: 8	M: 6 F: 13	-	Platelet & Plasma	BCA protein assay	Genetic marker	*Values based on Peak area <u>ADAM10 (Platelet)</u> CI: 0.5 times lower (0.47) than controls (0.9) Frailty: 0.6 times lower (0.54) than controls (0.9) *No significant difference between CI (0.47) vs frail + CI (0.47) ($p = 0.346$). <u>ADAM10 (Plasma)</u> CI: 1.3 higher (1.7) than controls (1.3) Frail: No difference (1.3) with controls (1.3) *No significant difference between CI (1.3) vs frail + CI (2.0) ($p = 0.316$). <u>Conclusion:</u> ↓ in platelets	(130)

										and ↑ in plasma in CI compared to healthy controls, regardless of the physical frailty condition.	
Italy	Cross-sectional study Mean age: 75.4	FC: 59 FI: 58 *M: 53 * F: 67	FC:61 FI:60	NA	NA	-	Plasma	ELISA	Inflammatory marker	FC: HtrA1 levels was 1.4 times higher in frail (73.0 ng/mL) compare to controls (50.4 ng/mL). FI: HtrA1 levels higher was 1.3 times higher in frail (68.0 ng/mL) compare to controls (53.5 ng/mL). <u>Conclusion:</u> HtrA1 levels ↑ in frail group compare to controls.	(131)
Italy	Cross-sectional study Mean age: 72.9 (controls) 76.9 (frail)	M: 37 F: 50	M: 43 F: 50	NA	NA	-	Plasma	HPLC & ELISA	Immune stimulation biomarkers	Neopterin: 1.7 times higher in frail group (25.80nmol/L) compare to controls (14.90 nmol/L). CRP: 1.7 times higher in frail group (3.79 nmol/L) compare to controls (2.12 nmol/L). Tryptophan: 0.8 times lower in frail group (51.31nmol/L) compare to controls (59.41 nmol/L). Nitrate: 0.3 times lower in frail group (0.67nmol/L) compare to controls (2.36 nmol/L). <u>Conclusion</u>	(96)

										(Neopterin, CRP, kyn/trp ratio) levels ↑ while tryptophan and nitrate levels ↓ in frail group compare to controls.	
China	Cross-sectional study Mean age: 69.6 (controls) 70.8 (pre-frail) 76.1 (frail)	M: 49 F: 96	M: 73 F: 88	NA	NA	3.5 years	Serum	ELISA	Inflammatory markers	MCP-1: 1.4 times higher in frail group (>250.91 pg/ml) compare to controls (185.03 pg/mL). MIP-1b: 1.4 times higher in frail group (>211.41 pg/ml) compared to controls (155.92 pg/mL). <u>Conclusion</u> MCP-1 and MIP-1b levels ↑ in frail group compare to controls.	(132)
Singapore	Prospective cohort study Mean age: 79.6 (controls) 75.8 (frail)	M: 30 F: 49	M: 5 F: 15	NA	NA	1 year	Serum	ELISA	Inflammatory markers	TNF-α: 2 times higher in frail group (1.30 pg/mL) compare to controls (0.60 pg/mL) at baseline. <u>Conclusion</u> TNF-α levels ↑ in frail groups compare to controls at baseline.	(133)
Turkey	Cross-sectional study Mean age: 72.70 (controls) 79.36 (frail)	M: 17 F: 27	M:14 F: 31	NA	NA	-	Serum	Solid phase sandwich ELISA	Metabolomic markers	α-klotho protein: 1.4 times higher in frail group (0.76 ng/ml) compare to controls (0.54 ng/ml). <u>Conclusion</u> ↑ α-klotho protein levels in frail compare to controls.	(134)
United Kingdom	Randomized control trial	1394	Frail (361) Pre-frail (520)	NA	NA	12 years	Whole blood	CRP & Clauss assay	Inflammatory markers	CRP: 1.3 times higher in frail/pre-frail (4.1 mg/L/3.7 mg/L) than in controls (3.2 mg/L)	(97)

	Mean age: 69 years	*Does not specify gender								Fibrinogen: 1.1 times higher in frail/prefrail group (3.6 g/L /3.3 g/L) than in controls (3.2 g/L). *Higher levels of baseline inflammation only shown significant associations with higher Frailty Index scores (scores increased on average by 0.030) overtime but not with Fried phenotype <u>Conclusion</u> CRP and fibrinogen levels ↑ in frail/pre-frail group compare to controls.	
Spain	Cross-sectional study Age 75–99 years	22 *Females only	60 Frail 22 Pre-frail	NA	NA	-	Serum	GC/MS	Nutritional markers	Levels of vitamin D: 0.6 times lower in frail/pre-frail (28 ng/mL/29 ng/mL) compare to controls (46 ng/mL). <u>Conclusion</u> Vitamin D levels ↓ among frail/pre-frail groups compare to controls.	(100)

Abbreviations: F, Female, M, Male, PF, Physical frailty, CI, Cognitive impairment, CF, Cognitive frailty, LC, Liquid chromatography, GC, Gas chromatography, HPLC, High Performance Liquid chromatography, MS, Mass spectrometry, FC, Fried's Criteria FI, Rockwood's frailty index, HDL, high-density lipoprotein, GGT, Gamma glutamyltransferase, ET, Ergothioneine, tHcy, Homocysteine, ADAM10, A Disintegrin and Metalloprotease Domain 10, HtrA1, HtrA High-temperature requirement serine protease A1, MCP-1, Monocyte chemoattractant protein 1, MIP-1b, Macrophage inflammatory protein-1-b, TNF-α, Tumour Necrosis Factor-α, CRP, C-reactive protein.

Table 3: Blood-derived CF biomarkers with their regulation, pathways and number of studies.

	Pathway	Biomarkers	Regulation	Number of studies	References
Amino acid metabolism	Glycine, serine and threonine metabolism	Tryptophan	↓	**2**	(95, 96)
		Guanidinoacetate	↓	1	(98)
	Arginine and proline metabolism	Creatinine	↑	1	(95)
		Guanidinoacetate	↓	1	(98)
	Arginine biosynthesis	Urea	↑	1	(99)
	Glutathione metabolism	GGT	↓	1	(99)
	Methionine metabolism / Biosynthesis of cysteine	tHcy	↑	1	(25)
	Histidine metabolism	Acetyl-carnosine	↓	1	(95)
		ET	↓	1	
Inflammatory response pathway	Complement and coagulation cascades / classical complement pathway	CRP	↑	**2**	(96, 97)
	Jak2/Stat pathway and NF-kB pathway	Neopterin	↑	1	(96)
	NF-kB pathway	α-klotho protein	↑	1	(134)
	Chemokine signaling pathway	MCP-1	↑	1	(132)
		MIP-1b	↑	1	(132)
	TNF signaling pathway	MCP-1	↑	1	(132)
		TNF-α	↑	1	(133)
Oxidative stress pathway	Lipid peroxidation	Malonaldehyde	↑	1	(3)
	Carotenoid biosynthesis	B-cryptoxanthin	↓	1	(98)
		Zeaxanthin	↓	1	(98)
	Insulin-like growth factor-1 signaling pathway	α-klotho protein	↑	1	(134)
Lipid metabolism	Cholesterol metabolism / steroid degradation	Cholesterol	↓	**2**	(98, 99)
	Cholesterol metabolism / steroid degradation	HDL	↓	1	(99)

Genomic stability	Cellular senescence / Signaling pathways regulating pluripotency of stem cells	Telomerase	↓	1	(3)
	Transforming growth factor beta signaling pathway	HtrA1	↑	1	(131)
Vitamin digestion and absorption	Cholecalciferol biosynthesis	Vitamin D	↓	**2**	(25, 100)
Metabolism of cofactors and vitamins	Ubiquinone and other terpenoid-quinone biosynthesis	α-tocopherol	↓	1	(98)
Glucose metabolism	Glucuronate pathway	UDP-glucuronate	↑	1	(95)
Signaling and cellular processes	Non-amyloidogenic pathway	ADAM10	↓	1	(130)
Energy metabolism	Nitrate–nitrite–nitric oxide (NO) pathway	Nitrate	↓	1	(96)
Platelet aggregation pathway	Platelet activation	Fibrinogen	↑	1	(97)

Abbreviations: Jak2/Stat, Janus Kinase/Signal Transducer and Activator of Transcription, NF-kB, nuclear factor kappa-light-chain-enhancer of activated B cells, HDL, high-density lipoprotein, GGT, Gamma glutamyltransferase, ET, Ergothioneine, tHcy, Homocysteine, ADAM10, A Disintegrin and Metalloprotease Domain 10, HtrA1, HtrA High-temperature requirement serine protease A1, MCP-1, Monocyte chemoattractant protein 1, MIP-1b, Macrophage inflammatory protein-1-b, TNF-α, Tumour Necrosis Factor-α, CRP, C-reactive protein.

of control group (96). Similarly, a randomised controlled trial reported that the baseline mean concentration of CRP was 1.3 and 1.2 times higher in frail and pre-frail groups, respectively (97). Moreover, this study found the high baseline mean concentration of CRP to be associated with increasing frailty index scores overtime. The study followed the participants for over 12 years and found that the scores among those with high baseline concentrations of CRP increased with an average of 0.03 over the years. CRP is a homopentameric acute-phase inflammatory protein that is elevated in inflammatory condition, certain cardiovascular diseases and infections (123). There is a close association between chronic inflammation and physical frailty (124). Cytokines and chemokines are the major culprits in the development of chronic inflammation and the immunosenescence process. Additionally, CRP is also involved in age-related pathogenesis (125). In respect to cognition, CRP is known to be elevated in diabetes, obesity, and smoking, all of which are risk factors common to stroke and dementia (126). This corresponds to a point before which inflammation plays an important role in mechanism underlying the risk of cognitive impairment and dementia (127). In a study of the Japanese population, it was reported that there was an association between higher CRP concentration and lower cognitive function, particularly in female participants (128). However, a meta-analysis study demonstrated that peripheral CRP level was weakly associated with global cognitive decline. This may be due to the small sample size and different methodologies (129).

3.4.1 Major pathways of the CF biomarkers

Figure 1 illustrates the regulation of blood-based CF biomarkers with their respective pathways. Overall, the blood-based CF biomarkers were predominantly involved in amino acid metabolism (25, 95, 96, 98, 99) and inflammatory response pathways (96, 97, 132-134).

3.4.1.1 Amino acid (AA) metabolism

AA metabolism include non-essential AA like arginine, glycine, serine, proline and cysteine as well as essential AA like glutathione, methionine, threonine and histidine (25, 95, 96, 98, 99). Dietary protein intake and circulating AA are essential for muscle plasticity and trophism (135, 136). They are also important for regulation of several biological processes such as inflammation, redox homeostasis and insulin sensitivity, all of which may be involved in age-related muscle atrophy and dysfunction (137, 138). As such, perturbed protein-amino acid metabolism may be indicative of physical frailty (139). Besides, AA also play integral roles within the CNS whereby they function as neurotransmitters, regulators of metabolism and also neuromodulators. Recent evidence suggests that these metabolic factors contribute to the neurodegenerative process, at least in the early stage in the pathogenic process (140-142). Amongst the non-essential AA group, it was found that specific methylated arginine analogues in the blood, specifically asymmetric dimethylarginine (ADMA), was involved in the pathogenesis of AD and late-life depression (143, 144). Furthermore, it was also found that arginine catabolism was altered in learning and memory centres in an aged brain (145). Glycine, on the other hand, possesses neuroactive properties and acts as a neurotransmitter (140). It can be synthesised from serine (146) which is associated with age-related cognitive decline. Glycine and serine influence the N-methyl-D-aspartate (NMDA) receptor activation which mainly regulates cognitive functions (147). Furthermore, regulation of neuronal protein serine and threonine is also thought to contribute to disorders of learning and memory (148).

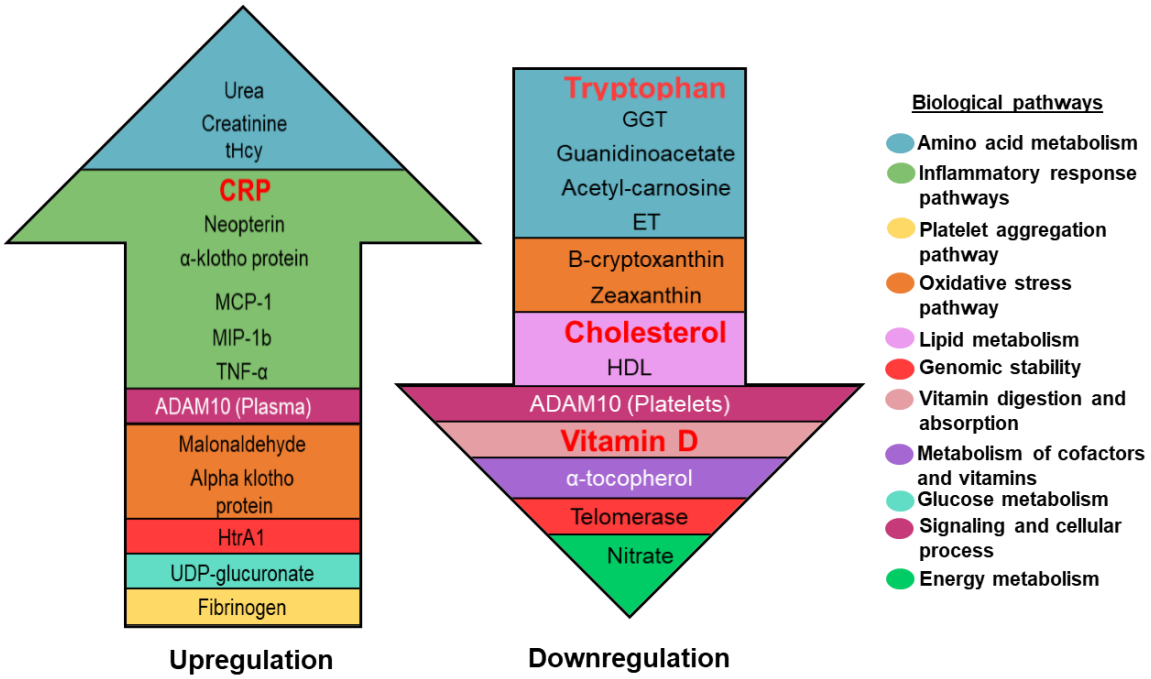

Figure 1: The regulation of blood-based CF biomarkers with their respective pathways.

In terms of physical frailty, the "Biomarkers associated with Sarcopenia and Physical frailty in Elderly persons (BIOSPHERE) study reported that older frail individuals were presented with elevated serum levels of asparagine, aspartic acid, citrulline, glutamic acid, sarcosine and taurine (139). Asparagine, aspartic acid, and glutamic acid were metabolised in resting muscles (149) whereas sarcosine altered myocyte quality control mechanisms (including autophagy) which may contribute to age-related muscle degeneration (150). Taurine, on the other hand, possesses osmoregulatory, anti-oxidant, and anti-inflammatory functions in the muscles (151, 152). Citrulline, an endogenous precursor of arginine, could activate the mammalian target of rapamycin complex 1 (mTORC1) (153).

As for the essential AA, they are associated with cognitive impairment and physical frailty. Notably, the essential AA cannot undergo de novo synthesis and are thus acquired through the diet. In terms of cognition, glutathione metabolism is thought to be altered in AD patients and its supplement is hypothesised to improve cognitive performance given its potent antioxidant and detoxifying actions (154). Likewise, histidine may aid in improvement of fatigue, enhance memory performance as well as improve clear thinking and attentiveness (155). Histidine is also hypothesised to alleviate the impairments induced by chronic cerebral hypoperfusion, a condition that could lead to dementia (156). Methionine, on the other hand, and its metabolite, homocysteine, are all linked to various degree of cognitive function, from mild cognitive decline to vascular dementia and AD (157). In fact, hyperhomocysteinaemia is an independent risk factor for cognitive dysfunction. Vascular damage caused by homocysteine has been implicated in vascular dementia, with an increased risk of multiple brain infarcts and dementia as homocysteine levels rise. In terms of physical frailty, low levels of essential AA were observed amongst older people severely affected by such condition (135,

139). These findings may indicate malnutrition, which is a common causative factor for frailty (158). This is supported by the fact that supplementation of glycine increased muscle mass by activation of mammalian target of rapamycin complex 1 (mTORC1) in C2C12 myoblasts (159). Likewise, dietary supplementation of both arginine and glutamic acid supressed the degradation of skeletal muscles by reducing the mRNA levels of genes involved in protein degradation (160).

3.4.1.2 Inflammatory response pathways

In physical frailty, it is said that inflammation has emerged as a compromised state of a dysregulated complex dynamical system (124). As such, prevalence and incidence of physical frailty have been associated with altered energy metabolism through both metabolic systems (161) and changes in musculoskeletal system function (162). Furthermore, the aggregate stress-response systems are also altered in physical frailty. Particularly, inflammation is consistently associated with frailty, with elevated levels of inflammatory mediators like CRP, interleukin (IL)- 6 and white blood cells such as macrophages and neutrophils, in a broad pattern of chronic, low-grade inflammation observed amongst those who are frail (163, 164). Chronic inflammation is commonly seen in the elderly population, whereby dysregulation of the immune response occurs, promoting maladaptive chronic low grade systemic inflammation (165, 166). In an acute inflammatory response, pro-inflammatory and anti-inflammatory cytokines act as a first-line defence mechanism against microorganisms, trauma, injury, toxins, or allergens (165). Normally, this intricate response would resolve by facilitating the elimination of pathogens, infected cells, and repair to damaged tissues (167). However, if the acute response were to persist, it would develop into a chronic inflammation, a long-term unresolved immune response (165).

The association of systemic inflammation with cognitive is also well documented. High serum levels of pro-inflammatory cytokines like IL-6, tumour necrosis factor alpha (TNF-α) and CRP not only impaired cognition (168), but also reduced processing speed (169), executive function (170) and memory (171). The associations between systemic inflammation and cognitive impairment have been reported across all age groups, including the young (172), middle-aged (173), and older adults (174). Amongst the older adults, the inflammation-cognition association has been found in generally healthy individuals (174, 175) and individuals with conditions like heart failure (176), dementia (177), and late-life depression (178). Systemic inflammation results in high levels of circulating pro-inflammatory cytokines that can interact with the CNS through three main routes. The first route is by pro-inflammatory cytokine transport proteins that limit active transport across the blood brain barrier (BBB), thus allowing central action (179). Next, stimulation of afferent nerves (e.g., the vagal nerve) whereby the stimulation transmits the currently heightened inflammatory status to lower brain stem regions (180). The last route is through reaching the circumventricular organs, which are located outside the BBB. Cells expressing toll-like receptors would then react to the increased inflammatory state, leading to further production and release of pro-inflammatory cytokines, which can then enter the brain through volume diffusion (180, 181). Stimulation of these three pathways causes the production of pro-inflammatory cytokines by microglia and astrocytes in the brain. These events disseminate signals throughout the neural

environment (181), resulting in comparable inflammation levels in the brain and the periphery (180). Elevated neuroinflammation can lead to structural and functional impairment in the brain (182), such as hippocampal atrophy (181, 182) and increased substantia nigra activity (172), both of which are associated with cognitive deficits (181-183).

4.0 Conclusion, limitations and future perspectives

The current review indicates that although the blood-based biomarkers like Trp, CRP, TC and vitamin D may be useful for diagnosis of CF, the results are inconsistent and it warrants further studies. Apart from the inconsistent results most of the previous studies evaluated either physical frailty or cognitive impairment. The majority of the biomarkers are associated with metabolism of AA and inflammatory response pathways, both of which are linked to physical frailty and CF. The present work also found that the platforms used for analysis of biomarkers varied between studies.

Acknowledgments

The present study acknowledges receipt of financial support from the Ministry of Higher Education Malaysia under the Long-Term Research Grant Scheme [600-RMC/LRGS 5/3 (002/2019)].

Conflict of interest

The authors declare no conflict of interest.

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