Lymphocytes' Count and Frailty

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Frailty is a geriatric syndrome characterized by a decrease in physiological reserve and reduced resistance to stress, as a result of an accumulation of multiple deficits in physiological systems. Frailty increases the vulnerability to adverse events and is associated with the aging process. Several studies show an association between frailty syndrome and altered blood lymphocyte levels in different clinical conditions, which is therefore potentially useful for monitoring interventions to improve or delay frailty at least in a subgroup of frail individuals.

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1. Introduction

Frailty is a clinical syndrome characterized by a decline in the multisystem functional reserve, which causes greater vulnerability to stressful situations and predisposes one to numerous adverse health effects including falls, hospitalization, disability, and mortality [1]. The prevalence of frailty increases with age [2], and an increasing number of frail older adults is expected due to the progressive aging of the population. Although frailty syndrome is classically associated with aging processes and most studies investigate it in older adults (age 65 years and older), different chronic conditions may promote frailty at earlier ages. For this reason, new interesting studies have also evaluated frailty in younger patients with cancer, diabetes, or coronary heart diseases [3][4][5]. Although numerous ways of measuring frailty syndrome have been described, the most widely accepted operational definition is one that considers frailty as a clinical syndrome that includes the presence of three or more of the following clinical criteria: Involuntary weight loss in the last year, muscle weakness, slow gait, self-reported fatigue, and low physical activity [5]

However, this or other instruments used to assess frailty have limited clinical utility, are time-consuming, are sometimes difficult to perform, and are sometimes not validated or sufficiently standardized [1]. In addition, they identify frailty late, once the clinical manifestations have started [5]. Existing evidence suggests that the physiological deterioration associated with frailty begins to be evident in a preclinical phase [3]. Its early detection would therefore help implement prevention and early intervention therapies in order to treat this syndrome and prevent related adverse results since it has been suggested that frailty could be reversible [6]. Accordingly, it is necessary to develop new tools that not only allow frailty to be identified in its early stages, including before symptoms occur but also the predisposition to develop this syndrome [7].

The search for frailty biomarkers that provide additional information to that obtained from clinical data has therefore become especially important in recent years [8]. Several studies have suggested that the inclusion of laboratory

data in frailty indexes could improve its prognostic power [9]. Ascertaining the pathophysiology of the disease is key to the development of frailty biomarkers. The pathophysiological mechanisms underlying the onset and development of frailty remain complicated and poorly understood, but chronic systemic inflammation has been considered one of the most important components contributing to its development [10][11]. In fact, several inflammatory mediators have been consistently associated with frailty [12]. Furthermore, immuno-senescence is believed to be involved in the development of the chronic inflammatory state related to frailty syndrome [12][13]. The main feature of immunosenescence is the change in the cellular composition of the T-cell compartment, which includes a decline in the number of naive phenotype cells and, conversely, an increase in the number of memory phenotype cells, all of which culminates in a proinflammatory state with greater production of cytokines, which leads to lower levels of cell proliferation and greater resistance to apoptosis [14]. One of the characteristic changes of the immune system with age is the alteration of the number and composition of different types of lymphocytes in the circulation. In older people, the number of CD4+ and CD8+ T lymphocytes and B lymphocytes is reduced, whereas the number of NK lymphocytes is increased compared to younger people. At the subset level, there is also a decrease in naïve T and B cells and an increase in memory T and B cells with aging. These changes may reflect a combination of reduced naïve lymphocyte production and accumulation of memory lymphocytes as a result of reduced overall lymphocyte production and host-environment interaction over time. As a result of these changes, older people are more vulnerable to infectious diseases and adverse outcomes when lymphocyte counts are lower [15]. Based on this, recent studies have associated frailty with alterations in the total lymphocyte count and lymphocyte subpopulations [3][16][17][18].

2. Relationship between Total Lymphocytes and Frailty Syndrome Prevalence

Several observational studies have analyzed the relationship between lymphocytes counts in blood and frailty syndrome as these cells represent an easy and cheap marker related to the chronic low-grade inflammatory state associated with frailty syndrome (**Table 1**). These studies evaluated frailty syndrome with Fried's criteria (14 studies), the Edmonton scale (one study), the Rockwood frailty index (one study), the Carolina frailty index (one study), the Frailty index containing 36 "health deficits" (one study), and the modified 11-item frailty index score (one study). With the exception of four studies, where no association was observed, they found that a lower total count or percentage of lymphocytes, even within the normal physiological range, is associated with higher rates of frailty and greater severity. However, the exclusion of men [19][20][21] and the relatively small sample sizes together with the lack of adjustment for possible confounding factors in the statistical analysis [22][23] could partially explain the discrepant results in these studies. The sex differences appear to be important when comparing studies performed only in men or in women, since the prevalence of frailty, although increasing with age in both males and females, is higher in females than in males. The presence of frailty had a negative impact on survival in both men and women, whereas mortality rates are higher in men than in women. Likewise, a multivariate analysis single-center observational study in patients with coronary artery disease showed that relative lymphocyte counts were inversely related to a higher risk of being frail, with an exponential increase in risk [18].

In both geriatrics research and clinical settings, the most-used definitions of frailty were developed by Fried and co-workers (physical frailty phenotype) and Rockwood and co-workers (the frailty index based on accumulative deficits). Among the studies analyzed in the review, the tools mostly used were the Fried model [10][12][13][16][17][18][20][23][24][25][26][27][28], which defines a phenotype that includes the presence of three or more of the following clinical criteria: Involuntary weight loss in the last year, muscle weakness, gait slow, self-reported fatigue, and low physical activity [5]. For their part, Gilmore et al. [29] assessed frailty using a modified version of Fried's frailty score, using four of the five available criteria (weakness, exhaustion, walking speed, and physical activity). Rockwood's frailty index focuses on the cumulative impact of a patient's clinical deficits identified by chronic diseases, signs, symptoms, and abnormal test results, allowing it to be quantified as a ratio (deficits present/total deficits considered) ranging from 0 to 1. In this context, the Rockwood frailty index (RFI) was calculated from 40 potential deficits (Collerton et al. [12]). Likewise, using the deficit accumulation index, several studies quantified frailty syndrome by means of shorter items' scales such as the Carolina Frailty Index (CFI) based on 36 items [21], an 11-item modified Frailty Index (mFI), and the Frailty index containing 36 possible "health deficits". Finally, a study applied the Edmonton Frailty Scale (EFS) to assess frailty [30]. This scale, an abbreviated assessment of the Comprehensive Geriatric Assessment, takes into account 10 domains (cognition, mood, functional independence, medication use, social support, nutrition, health attitudes, continence, burden of medical illness, and quality of life); its maximum score is 17 and represents the highest level of frailty [31].

The relationship between total lymphocyte counts and frailty percentages has also been evaluated in three longitudinal studies conducted in cancer patients [28][29] and institutionalized older women [32]. However, only one of them validated the associations observed in cross-sectional studies, showing that in addition to being associated with frailty at the beginning of the study, low lymphocyte counts predicted its progression at one year of follow-up, with a moderate sensitivity of 65.2% and a specificity of 68.7% [28].

A reduction in total lymphocyte count in blood is believed to be a characteristic marker of deleterious changes in the immune system associated with aging [33], and lymphocyte counts tended to decrease with age [34]. However, recent studies indicate that nearly every component of the immune system undergoes dramatic age-associated restructuring, leading to changes that include both enhanced as well as diminished function depending on the subtype of immune cells and their location [35]. Indeed, the emerging consensus is that immunological aging is part of a continuum of developmental processes, encompassing complex reorganizational events, compensatory mechanisms, and qualitative alterations in function. Confirming this, our analysis showed that only some of the subtypes of lymphocytes are associated directly or inversely associated with frailty syndrome.

Table 1. Main characteristics of clinical studies analyzed in frailty patients.

Reference Sorted by Year of Publication	Study Design	Sample Size (*n*)	Subjects (Sex and Age)	Participants	Frailty Assessment	Relationship between Total Lymphocyte Count and Frailty
Semba et al., 2005 [20]	Case-control study.	122	Community dwelling-women (cases) who died during 5 years of follow-up (mean age 76.9 ± 6,4 years) and women (controls) matched by age, frailty, and morbidities who survived during 7 years of follow-up (mean age 77.3 ± 6.8 years).	Community-dwelling adults.	Fried's criteria.	There were no significant differences in counts or percentages of lymphocytes between frail, pre-frail, and non-frail women.
De Fanis et al., 2008 [23]	Case-control study.	26	22 women and 4 men with a mean age of 83.8 ± 5.3 years (range 72–94).	Community-dwelling adults.	Fried's criteria	No significant differences in total lymphocyte counts between frail and non-frail participants were observed.
Leng et al., 2009 [10]	Observational cohort study.	1106	Women from the WHAS I cohorts with an age range of	Community-dwelling woman.	Fried's criteria.	No significant association between total counts of

Reference Sorted by Year of Publication	Study Design	Sample Size (*n*)	Subjects (Sex and Age)	Participants	Frailty Assessment	Relationship between Total Lymphocyte Count and Frailty
			65–102 years and women from the merged WHAS I and II cohorts with an age range of 70–79 years.			lymphocytes with frailty was identified.
Collerton et al., 2012 [12]	Cross-sectional study.	845	Different cohorts with a percentage of women in each cohort ranging from 60 to 75%. All participants were over 85 years old.	Community-dwelling or institutionalized older people.	Rockwood frailty index and Fried's criteria.	The total lymphocyte count was inversely related to both measures of frailty, Fried scale and the Rockwood frailty index.
Fernández-Garrido et al., 2014 [16]	Cross-sectional study.	42	Women with an average age of 84.2 (±6.5) years (range, 70–99 years).	Non-demented institutionalized older population.	Fried's criteria.	There was a significant and inverse relationship between the number of fulfilled frailty criteria and the lymphocyte count.

Reference Sorted by Year of Publication	Study Design	Sample Size (*n*)	Subjects (Sex and Age)	Participants	Frailty Assessment	Relationship between Total Lymphocyte Count and Frailty
Nishijima et al., 2017 [21]	Cross-sectional study.	133	54 women and 79 men with a median age of 74 years (range 65–92).	Cancer patients.	36-item CFI.	Although the lymphocyte count in isolation was not related to frailty, the NLR was positively correlated with the frailty. Patients with a higher NLR also had increased odds of being frail/pre-frail.
Hou et al., 2018 [36]	Cross-sectional study.	345	154 women and 191 men with a median age of 71.0 years (IQR 65.0–77.0 years).	Elderly patients with coronary heart disease, (ACS (83.6%) and single-vessel disease (66.4%)).	Fried's criteria.	A significant positive correlation was observed between NLR and the frailty score, and increased odds of being frail.
Fernández-Garrido et al., 2018 [32]	Two-year follow-up study.	94	Women with an average age of 82 (±7) years.	Non-demented institutionalized older women.	Fried's criteria.	There was a significant inverse correlation between the frailty scores and lymphocyte counts at

Reference Sorted by Year of Publication	Study Design	Sample Size (*n*)	Subjects (Sex and Age)	Participants	Frailty Assessment	Relationship between Total Lymphocyte Count and Frailty
						baseline, but not at follow-up.
Bernabeu-Wittel et al., 2019 [27]	Multicenter cohort study.	444	200 women and 244 men with an average age of 77.3 (±8.4) years.	Community-dwelling (93.7%) and institutionalized (6.3%) older patients (outpatients in the Internal Medicine and Geriatric areas).	Fried's criteria.	The combined presence of frailty and sarcopenia was associated with a lower lymphocyte count.
Wilson et al., 2019 [19]	Observational cohort study.	377	185 women and 192 men with an average of 73.7 years (range, 50–98 years).	Patients hip fracture.	Modified 11-item frailty index score.	Total lymphocyte count weakly inversely correlated with frailty.
Navarro Martínez et al., 2019 [37]	Cross-sectional clinical trial.	46	Men with an average age of 72.2 (±9.4) years (range, 51–92 years).	Patients with prostate cancer undergoing antiandrogen therapy.	Fried's criteria.	The lymphocyte counts were significantly lower in both frail and prefrail individuals than in robust individuals.

Reference Sorted by Year of Publication	Study Design	Sample Size (*n*)	Subjects (Sex and Age)	Participants	Frailty Assessment	Relationship between Total Lymphocyte Count and Frailty
Marcos-Pérez et al., 2019 [38]	Cross-sectional study.	259	174 women and 85 men with an age range of 65–102 years.	Patients were contacted through associations of older or retired people, day care centers, and nursing homes.	Fried's criteria.	The relationship between frailty and lymphocyte count was not studied in isolation.
Núñez et al., 2020 [18]	Observational study.	488	200 women and 188 men with an average age of 78 (±7) years.	Patients surviving an episode of an ACS.	Fried's criteria.	The low percentage of lymphocytes was associated with frailty and a higher risk of being frail.
Buigues et al., 2020 [28]	One-year follow-up study.	39	Men with an average age of 71.9 (± 9.8) years.	Patients with prostate cancer undergoing antiandrogen therapy.	Fried's criteria	At baseline lower lymphocytes count were significantly correlated with the frailty syndrome severity and predicted its progression at one year of follow-up.
Samson et al., 2020	Observational cohort study.	289	144 women and 145 men	Elderly people.	Frailty index	The relationship between frailty

Reference Sorted by Year of Publication	Study Design	Sample Size (*n*)	Subjects (Sex and Age)	Participants	Frailty Assessment	Relationship between Total Lymphocyte Count and Frailty
[39]			between 60–87 years of age.		containing 36 possible "health deficits".	and the total lymphocyte count was not studied (they studied separately subpopulations of T cells, B cells, NK cells counts).
Bodolea et al., 2020 [26]	Observational cohort study.	179	101 women and 78 men with an average age of 65.07 (±12.9) years (range, 23–90 years).	Patients with cardiovascular disease	Fried's criteria.	Lower lymphocyte count and NLR were significantly correlated with the frailty syndrome and its severity.
Bilgin et al., 2021 [30]	Observational cohort study.	108	57 women and 51 men. Median ages of the frail and non-frail groups were 65 (50–78) years and 62 (50–79) years, respectively.	Patients with type 2 diabetes mellitus.	Edmonton Frail Scale.	Elevated MPVLR were significantly correlated with the frailty syndrome and its severity.
Gilmore et al., 2021 [29]	Longitudinal cohort study.	581	Women. Age range, 22–81	Women with stage I-IIIC	Fried's criteria	Low lymphocyte counts and the

of T follicular helper (TFH) cells in aging: Influence on the immune frailty. Ageing Res. Rev. 2020, 61, 101071.

Reference Sorted by Year of Publication	Study Design	Sample Size (*n*)	Subjects (Sex and Age)	Participants	Frailty Assessment	Relationship between Total Lymphocyte Count and Frailty
			years.	breast cancer.	modified	NLR were associated with post-chemotherapy frailty, as well as changes in frailty from pre-chemotherapy to post-chemotherapy.

ACS: Acute coronary syndromes; CFI: Carolina Frailty Index; IQR: Interquartile range; MPVLR: Mean platelet volume/lymphocyte ratio; NLR: Neutrophil to lymphocyte ratio; WHAS: Women's Health and Aging Study.

3. Relationship between Lymphocyte Subtypes and the Presence of Frailty Syndrome and Its Severity

Five studies (**Table 2**) evaluated the relationship between the severity of frailty syndrome and the blood counts of lymphocyte subpopulations in community-dwelling older adults. They found an association between frailty and increased numbers of CD8+ lymphocytes [12][17][20] and in the CD8+CD28-lymphocyte ratio and with a lower count of lymphocyte CD4+/CD8+ ratio [20], which represents a marker of aging of the immune system [39][40]. Interestingly, both frailty and cytomegalovirus seropositivity were associated with an increase in CD8+ T-lymphocytes. An epidemiological study suggested that CMV-seropositivity is an independent risk factor for frailty in older women [41]. The increased ratio between memory and naïve CD8 T cells was replicated using both Fried's and Rockwood's frailty scale in community-dwelling older adults in the Newcastle 85+ study [12]. In contrast, the memory/naïve CD4 T cell ratio, the CD4/CD8 T cell ratio, and the memory/naïve B cell ratio were not significantly associated with frailty syndrome in this study when their blood counts were compared with the severity of frailty measured by Fried's scale, and the results partially overlapped when Rockwood's frailty index was also taken into account [12]. The association between frailty syndrome and B cell counts was only reported in two studies, with the Rockwood frailty scale in one study [12] and Fried's scale in another one [17]. In a subcohort study performed in older adults belonging to the Doetinchem cohort study in the Netherlands, the frailty syndrome was associated with some lymphocyte subpopulations among the 37 subpopulations studied [30]. Frailer women, but not men, showed fewer T lymphocytes, and CD56+ T cells in particular [30], which are known for their cytotoxic capacity [22]. This result is consistent with another study reporting an increased expression of CD56 in lymphocyte T cells from individuals

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with better cognitive and physical function [42]. Frailty syndrome was also associated with significantly fewer late differentiated CD4+ TemRA T cells in older frail women and represent a subset of effector memory T cells expressing CD45RA (termed TEMRA) after antigenic stimulation, which display a transcriptional and proteomic program with cytotoxic features [42]. Cells in the immune system that express receptors for chemokines participate in the regulation and effectors of the immune system. The expression of different chemokine receptors has been associated with Th1 and Th2 lymphocyte phenotypes, with Th1 cells expressing CXCR3 and CCR5, while Th2 cells express CCR3 and CCR4 [43]. Frailty syndrome has also been associated with an increase in some subpopulations of T lymphocytes expressing a subtype of CCR receptors. In fact, higher concentrations of total CCR5, CCR5-CD8, and CCR5-CD45RO T cells (called "memory" lymphocytes) have been described in frail older adults than in non-frail controls [26], suggesting a significant expansion of a specific subset of T cells with a proinflammatory type 1 phenotype [44]. CC chemokine receptor 5 (CCR5) interacts with CCL3, 4, 5, and 8 chemokines, and plays an important role in the regulation of leukocyte recruitment, trafficking, and immune activation [45]. CCR51 T lymphocytes have been shown to have a proinflammatory type 1 phenotype, and CCR5+ T lymphocytes can significantly contribute to several inflammatory conditions such as frailty syndrome and related adverse outcomes [23][46].

Table 2. Lymphocyte subtypes and their relationship with frailty.

Reference Sorted by Year of Publication	Study Design	Sample Size (*n*)	Subjects (Sex and Age)	Disease/Patients	Frailty Definition	Lymphocyte Subtypes Studied	Relationship between Lymphocyte and Subtypes Count and Frailty
Semba et al., 2005 [20]	Case-control study	61 women who died (cases) to 61 women who did not die (controls) during follow-up were matched	Women (cases) with a mean age of 76.9 (6.4) years and women (controls) 77.3 (±6.8) years.	Community-dwelling adults.	Fried's criteria.	Counts or percentages of CD4+, CD8+, CD4+CD28-, CD4+CD28+, CD8+CD28-, CD8+CD28-, CD4+CD45RA+, CD4+CD45RO+, CD8+CD45RA+, CD8+CD45RO+ T cells and CD4/CD8 T cells ratio.	Frail women appeared to have significantly higher CD8+ and CD8+CD28− lymphocyte counts. Frail women also had significantly lower CD4+, lower CD4+CD28+, higher CD8+, higher CD8+CD28-,

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Reference Sorted by Year of Publication	Study Design	Sample Size (*n*)	Subjects (Sex and Age)	Disease/Patients	Frailty Definition	Lymphocyte Subtypes Studied	Relationship between Lymphocyte and Subtypes Count and Frailty
							and lower CD8+CD28+ percentages
De Fanis et al., 2008 [23]	Case-control study	26 frail and no frail participants were matched.	84,6 % were women and 15.4% men with a mean age of 83.8 ± 5.3 years (range 72–94).	Community-dwelling adults.	Fried's criteria	Counts of CD3+, CD4+, CD8+, CD45RO+,CD45RO-, CCR5+, CCR5+ CD4+, CCR5+CD8+, CCR5+CD45RO+ and CCR5+CD45RO-T cells.	Frail participants had higher CCR5+, CCR5+CD8+, and CCR5+CD45RO-T-cell counts than matched non-frail controls.
Collerton et al., 2012 [12]	Cross-sectional study	845 patients.	+85 year old.	Community-dwelling or institutionalized older people.	Rockwood frailty index and scale Fried.	Count and ratios of CD4/CD8 T cells, memory/naïve CD4 and CD8 T cells and memory/naïve B cells.	High levels lymphocytes memory/naïve CD8 T cell ratio were associated with a lower risk of frailty on the Fried scale and low levels of memory/naïve B cells were associated with a higher risk of frailty on the

Reference Sorted by Year of Publication	Study Design	Sample Size (*n*)	Subjects (Sex and Age)	Disease/Patients	Frailty Definition	Lymphocyte Subtypes Studied	Relationship between Lymphocyte and Subtypes Count and Frailty
							Rockwood frailty index.
Marcos-Pérez et al., 2019 [38]	Cross-sectional study	259 patients.	85 male and 174 female with an age range of 65–102 years.	Patients were contacted through associations of older or retired people, day-care centers, and nursing homes.	Fried's criteria.	Percentages of CD3+, CD4+ and CD8+ T cells, CD19+ B cells, CD16+56+ NK cells and CD4/CD8 T cells ratio.	A significant increase in the CD4+/CD8+ ratio and a significant decrease in the % CD19+ cells were observed in the frail group.
Samson et al., 2020 [39]	Observational cohort study.	289 patients.	145 men and 144 women between 60–87 years of age.	Elderly people.	Frailty index with incorporates 36 possible "health deficits"	The numbers of CD16 and CD56 NK cells, CD56+ T cells and CCR7 + CD4 +/CD8 T cells, which were classified as naïve (CCR7+CD45RA+) or central memory (CCR7 + CD45RA-) T cells. CCR7-CD4 +/CD8 + T cells were divided into effector memory T cells (Tem, CCR7-CD45RA-) and effector memory T cells that re-express CD45RA T	More frail women, but not men, showed fewer CD56 + T cells and fewer CD4 + TemRA cells.

Reference Sorted by Year of Publication	Study Design	Sample Size (*n*)	Subjects (Sex and Age)	Disease/Patients	Frailty Definition	Lymphocyte Subtypes Studied	Relationship between Lymphocyte and Subtypes Count and Frailty
						cells (TemRA, CCR7-CD45RA +).	

4. Conclusions

A lower total count or percentage of lymphocytes has been associated with frailty and its severity in different populations of older adults. These findings provide additional support for theories linking inflammation to frailty and provide insight into the potential roles of lymphocytes in the pathogenesis of frailty. Likewise, the inclusion of this common analytical parameter in traditional frailty indices could help to identify frailty, even at an early stage, and its monitoring would enable assessment of the progression of frailty and the response to the applied interventions.