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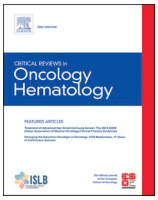

Biomarkers in blood and saliva to screen fragile patients with solid tumors: A systematic review of the literature

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ABSTRACT

Objective: Frailty is a multidimensional syndrome. It necessitates individualized therapies, particularly in oncological surgery, due to the increased risk of perioperative complications in frail patients. Recent literature suggests that biomarkers in saliva and blood may serve as valuable tools in clinical practice. To identify effective methods for screening frail patients with solid tumors using appropriate biomarkers, we conducted a systematic review of the literature.

Methods: A comprehensive literature search was conducted in Pubmed, Cochrane Library and Web of Science from the inception until 5th February 2024. Our inclusion criteria mandated a clear definition of frailty and a significant association with specific biomarkers in saliva or blood in patients with solid tumors.

Results: From 2604 screened abstracts 17 publications were included in the analysis. The results regarding biomarkers that were significantly associated with frailty, varied across the studies. Regarding frailty instruments, the G-8 geriatric screening tool and the Fried scale were the most frequently used tools. Both, elevated levels of CRP and IL-6 correlated with frailty in some research, while other studies identified links with the neutrophil-lymphocyte ratio, amino acids, or immune cells. Notably, no salivary biomarkers for frailty were found in patients with solid tumors.

Conclusion: There are currently no established blood or salivary biomarkers for frailty. However, an elevated inflammatory status and related markers are often significantly correlated with frailty in solid tumor patients. These findings highlight the potential to develop suitable biomarkers for frail oncology patients, emphasizing the need for further research in this area.

1. Introduction

As our society is aging, the rate of tumor disease, especially in older patients, is steadily increasing, and so is the rate of oncological correct, but high-risk surgical therapies (Parks and Cheung, 2022). The postoperative outcome of cancer patients following surgical therapy is dependent on several patient-specific factors. Above all, age and previous illnesses play a role. Cancer and cancer therapies can lead to the early development of frailty, a geriatric syndrome that indicates a decline in multiple body systems and is often fatal. Frailty is defined as "the diminished physical capacity with progressive physical decline," according to Fried et al. (2001). The prevalence of frailty varies among cancer survivors and is associated with an increased risk of mortality, especially with solid tumors (Harneshaug et al., 2019; Lealdini et al., 2015).

This individual susceptibility of older cancer patients should underpin preoperative decision making to adapt therapeutic approaches, particularly to individualize surgical radicality and improve preoperative and postoperative morbidity. Here, geriatric oncology primarily uses simple screening tools to identify clinically fragile patients who will benefit from intensive multidisciplinary Comprehensive Geriatric Assessment (CGA) (Parker et al., 2018). The preoperative assessment of the health status and thus individual therapy-related influences and side effects, are of great economic importance. In addition to geriatric assessment tools, biomarkers can be a further option for screening fragile patients in order to obtain a preoperative risk assessment for the

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individual patient with regard to perioperative complications (Berben et al., 2021).

In recent years, there has been increasing research on biological backgrounds of frailty. A growing number of studies have identified a link between frailty syndrome and changes in peripheral inflammatory markers (Navarro-Martínez et al., 2019). Underlying biological causes of frailty are diverse. Among other things, inflammatory processes, changes in the microbiota and metabolic disorders are known to play a role (Gilmore et al., 2021; Navarro-Martínez et al., 2019).

Markers from body fluids, which are validated by laboratory chemistry, are gaining importance as a potential method for predicting morbidity and mortality in older adults and thus for pretherapeutic risk evaluation (Gilmore et al., 2021). Appropriate biomarkers could therefore be used for pre-therapeutic risk stratification, as well as for disease detection.

Frailty is a multifactorial syndrome with neuroendocrine and inflammatory components (Song et al., 2009). Many possible biological markers have been proposed, but so far there is no typical laboratory profile for frailty. However, elevated levels of interleukin-6 (IL-6) and C-reactive protein (CRP) correlate with low body mass index (BMI) and frailty (Buigues et al., 2020).

In order to be able to validate suitable biomarkers, serum samples in particular were considered the means of choice. For some time, biomarkers for frailty in saliva have also been described. In recent years, salvia in particular has attracted attention as its use offers practical advantages over simple material collection, constant availability and cost effectiveness. In particular, the possibility of dispensing with an invasive measure for the use of biomaterial represents an advantage through the measurement of biomarkers in saliva (Furtado et al., 2020).

The determination of suitable biomarkers in cancer patients before the start of therapy is intended to increase the chances of recovery and quality of life of fragile patients by recommending prehabilitation and creating an adapted therapy plan based on individual performance. The general aim is to modify current treatment guidelines and thus establish a standardized therapy algorithm that is adapted to the individual requirements of elderly, multimorbid patients in the future.

To this end, this review examines the extent to which the literature can already make statements on the significance of biomarkers in blood and saliva in fragile patients with solid tumors.

2. Methods

2.1. Literature search and eligibility criteria

This systematic review is based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (1). It is registered at PROSPERO (CRD42024517519).

The following electronic databases were searched: MEDLINE (PubMed), Cochrane Central Register of Controlled Trials (Cochrane Library) and Web of Science Core Collection (Clarivate) from inception until 5th February 2024.

The reproducible searches for all databases are available in the EXCEL file see Appendix 1.

Duplicates were removed by the librarian (LCO) using the automation tool The Deduplicator (https://pubmed.ncbi.nlm.nih.gov/32004673/). Grey literature, such as conference abstracts, were not included. We imposed no language or other restrictions on any of the searches. Furthermore, studies included in related systematic reviews and meta-analyses were screened for eligibility.

Study inclusion criteria for review were studies and reports of biomarkers for frailty in serum and saliva in humans. Frailty in our included studies must have been clearly defined with a validated measure method. Saliva and/ or blood biomarker must be reported with saliva/ serum levels. Saliva and/ or blood biomarker must have demonstrated statistical significance in association with frailty (p-values <0.05). Patients must be oncological patients with solid tumors (no tumors of the blood, bone marrow, lymph nodes).

The exclusion criteria were missing clear diagnostic criteria for frailty, as well as missing data on quantitative levels of biomarkers in saliva and blood. Meta-analyses, systematic reviews, literature review and case reports were not included. Results should be interpreted accordingly. Only the latest published data were reported in case of articles that were an update of previously published patients.

2.2. Data extraction

Title and abstract screening, as well as full-text screening, were conducted by two review authors (S.H. and V.C.L.) independently. A third independent reviewer (W.B.) was contacted in case of disagreements between the first two reviewers. Data extraction was performed by S.H. and re-checked independently by V.C.L. using a predefined EXCEL spread sheet. The following information was collected: type of tumor, undergoing therapy, frailty instruments, examined biomarkers and biomarkers with significant correlation with frailty.

2.3. Risk of bias assessment

The risk of bias of each study was assessed by each reviewer using an adapted version of a standardized quality assessment tool, in this case the Newcastle-Ottawa Scale (NOS) (Stang, 2010), see Appendix 2. The NOS can be used for both case-control and longitudinal (prospective) studies. Cross-sectional studies were assessed as case-control studies. The NOS evaluated three quality parameters—selection, comparability, and outcome across eight specific items, with slight variations in scoring between case-control and longitudinal studies (Luchini et al., 2017), see Appendix 2.

2.4. Data synthesis and analysis

A descriptive analysis was performed. A metanalysis was not possible due to the heterogeneous data.

3. Results

3.1. Study selection

A total of 2602 records were retrieved form the three databases. 417 reports were removed as duplicates from the databases before the start of the screening. Two reviewers (V.L. and S.H.) independently screened 2185 titles and abstracts, of which 2160 reports were deemed irrelevant. 25reports were retrieved for full-text review. 9 of these reports were excluded: 6 of them did not define frailty clearly, 3 did not find significant results in the correlation of frailty and biomarkers in saliva or blood. One additional article was identified through screening references of relevant reviews using the search criteria (Falandry et al., 2015). In total, 17 full-text articles were included in the review. Further details are shown in the PRISMA flowchart in Fig. 1 (Page et al., 2021).

3.2. Study and participant characteristics

Characteristics of the included studies are presented in Table 1. All 17 studies were observational study designs. 7 studies were longitudinal cohort studies, 7 were cross-sectional studies and 3 were case-control studies. Across the 17 studies, a total of 3729 participants were included. Breast cancer was the most frequently examined solid tumor, followed by prostate cancer. Cancer stages varied widely, ranging from stage I to IV (localized to metastatic), with the majority of studies commencing at the pre-treatment phase. Out of the studies that included participants receiving treatment ($n = 6$, 43 %), two prostate cancer studies involved patients on androgen deprivation therapy (ADT), while three breast cancer studies had patients undergoing adjuvant or neoadjuvant chemotherapy and/or hormone therapy.

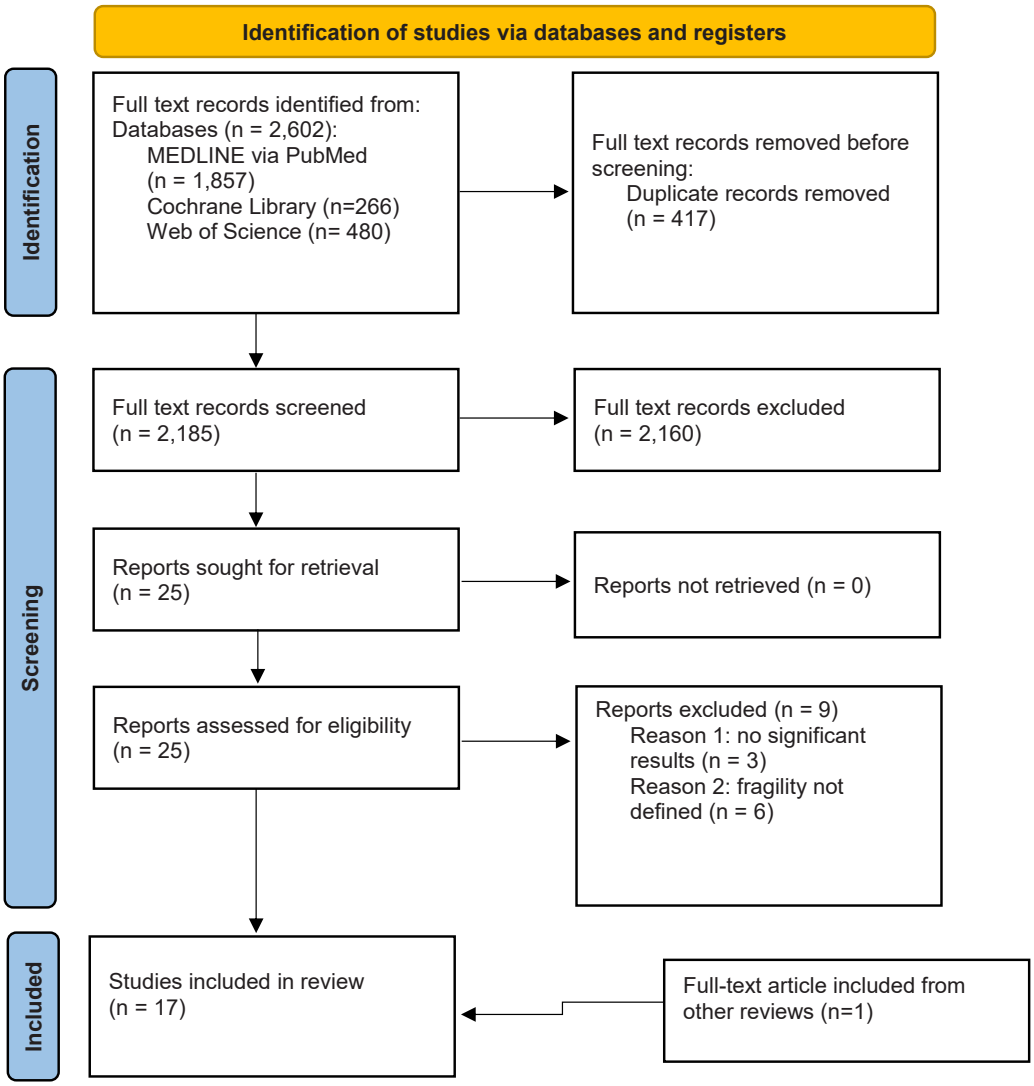

Fig. 1. PRISMA flow diagram for new systematic reviews which included searches of databases and registers only.

Two studies (Buigues et al., 2020) and (Navarro-Martínez et al., 2019) evaluated the association during treatment. Another study compared the association in patients eligible for adjuvant systemic chemotherapy with patients not eligible for systemic chemotherapy, but only for endocrine treatment (Dalmasso et al., 2018). Gilmore and co-authors examined pre-treatment cytokine levels to predict frailty after treatment, without assessing this at every time point (Gilmore et al., 2021). Most of the other studies examined the association in patients pretreatment or after chemotherapy.

3.3. Assessments of frailty

The measurements of frailty varied significantly across the 17 studies. The most frequently used instrument was the G-8 score (n = 5) (2,7,8,9,13 in Table 1) (Bellera et al., 2012). "Fit" was defined as a total score above 14 points, while "frail" was defined as a total score of 14 points or lower. In three of the studies, the Fried Frailty Phenotype (FFP) was utilized (1, 12, 15 in Table 1). "Frailty" was defined based on specific criteria, and applicable points were added, consisting out of components like self-reported weakness, exhaustion, walking speed and physical activity. The total scores of the participants ranged from 0 to 4, where 0 was the lowest and 4 the highest frailty measure (Gilmore et al., 2020).

In eight studies, frailty was measured as a deficit accumulation index or geriatric vulnerability score, with two studies using the Leuven Oncogeriatric Frailty Score (4, 13 in Table 1), two others using Balducci criteria (13, 16 in Table 1), one study using the Edmonton Frailty Scale (Lealdini et al., 2015), and another using the Carolina Frailty Index (Nishijima et al., 2017). One study utilized the Balducci frailty category in conjunction with the Leuven Oncogeriatric Frailty Score (Dalmasso et al., 2018).

3.4. Blood-based biomarkers

In all 17 studies, peripheral circulating blood markers were measured. The statistically significant results found in this review (p-values < 0.05) are presented below and categorized into the following groups: inflammatory markers, acute phase reactants, microRNAs, T-lymphocytes and telomere length.

3.5. Saliva-based biomarkers

According to our inclusion criteria, no salivary biomarkers to screen frail patients with solid oncological tumors were found in the literature.

3.6. Inflammatory markers: cytokines, cytokine receptors, and acute phase reactants

Cytokines, cytokine receptors, and acute phase reactants associated

Table 1
List of included publications.

Reference	Cases (n)	Type of Tumor/ Therapy	Frailty instruments	Investigated biomarkers	**Biomarkers with significant correlation with frailty**
1 Navarro-Martínez et al. (2019)	46	Prostate cancer/ androgen deprivation therapy	Fried scale. A geriatric assessment was performed, based on the Minimental State Examination for cognitive function, the Barthel index for basic activities of daily living, the Yesavage scale for geriatric depression, and the Athens insomnia scale	leukocyte differential count, IL-beta, TNF-a, IL−6, IL−8, fibrinogen, CRP	**Low lymphocyte count, IL−6, CRP, and fibrinogen**
2 Wu et al. (2023)	119	Breast cancer (TNBC, LumB-like breast cancer)/ Before therapy	G8- Score, full geriatric assess- ment	Serum MMA concentrations	**significantly higher MMA levels**
3 Rønning et al. (2010)	187	colon or rectum/ 14 days before elective resec- tions	pre- operative CGA	CRP, IL−6, TNF-α and D-dimer	**CRP, IL−6, TNF-α and D-dimer**
4 Brouwers et al. (2015)	82 young and 162 older non-metastatic breast cancer patients	Non- metastatic Breast cancer/ Different TNM-Levels, partly after neoadjuvant CT	Leuven Oncogeriatric Frailty Score (LOFS)	leukocyte telomere length (TL) and plasma levels of IL−6 regulated upon activation, normal T cell expressed and secreted (RANTES), MCP-1, IGF-1	**IL−6 plasma levels**
5 Nishijima et al. (2017)	133	Breast Lung Genitourinary Gastrointestinal Other ≧ 65 years / before initiation of therapy	36-item Carolina Frailty Index (CFI)	lymphocyte monocyte ratio; neutrophil lymphocyte ratio; platelet lymphocyte ratio; white blood cell	**High** neutrophil lymphocyte ratio
6 Buigues et al. (2020)	46	Prostata cancer / Undergoing Antiandrogen Therapy	three or more of the following components: low lean mass, weakness, self-reported exhaustion, low activity level, andslow walking speed; prefrailty was defined as having one or two of those components	IL−1beta, IL−6, IL−8, TNF alpha, CRP and leukocytes	**high IL−6 levels, low lymphocyte counts in blood, IL−8, monocyte counts, CRP**
7 Berben et al. (2021)	65	Early Luminal Breast Cancer, early invasive hormone- sensitive, HER2-negative, grade II or III / planned for surgery	G8-score	plasma levels of IGF−1, IL−1α; IL−1β; IL−6; IL−10; IL−12p70; IL−17A; IL-17F; IL−27; INFγ;; TNFα and TGF-β1, chemokines (interferon gamma-induced protein 10 (IP−10); IL−8 and MCP−1), immune check- point proteins (sCD25; 4–1BB; CD86; cytotoxic T-lymphocyte-associated protein 4 (CTLA−4); PD-L1; PD−1; T-cell immunoglobulin and mucin domain-containing molecule 3 (TIM−3); lymphocyte-activation gene 3 (LAG−3); galectin (Gal−9); sCD27; PD-L2) and CRP levels of 20 immune related plasma miRNAs (let−7e, let−7i, miR−9, miR−17, miR−18a, miR- 19a, miR−19b, miR−20a, miR−21, miR−92a, miR−125b, miR−126, miR−146a, miR−150, miR−155, miR−181a, miR−195, miR−223, miR−326 and miR−424) isolated T-cells, the expression level of $P16^{INK4a}$	**TIM−3, miR−19b and T-cell $P16^{INK4a}$** **TIM−3, plasma microRNAs (miR−19b and let−7i), CM $CD4^+$ cell subsets, NK-related cell subsets and T cell $p16^{INK4a}$**
8 Burgassi et al. (2021)	603	Colorectal Breast Lung Liver Digestive non-colorectal Genital or urinary tract Haematological malignancies Skin, melanoma Prostate Other * / undergoing geriatric assessment before therapeutic decisions	G8- Score	CAR	**higher values of CAR**
9 Berben et al. (2020)	65	Early invasive luminal breast cancer (hormone sensivitve, Her2- negative)	G8-score	immune/ senescence profile [IL−1a; IL−1b; IL−6; IL- 10; IL−12p70; IL−17A; IL-17F; IL−27; interferon gamma (INF-γ; TNFα and	**Low $CD8^+$ cells expressing CD27 or CD28, double-positive $CD27^+CD28^+$ cells; Increased double-negative**

(*continued on next page*)

Table 1 (*continued*)

Reference	Cases (n)	Type of Tumor/ Therapy	Frailty instruments	Investigated biomarkers	**Biomarkers with significant correlation with frailty**
				free active TGF−β1], plasma chemokines (i.e. IP−10; IL−8; MCP−1), immune checkpoint proteins [sCD25; 4–1BB; CD86; cytotoxic T-lymphocyte-associated antigen 4 (CTLA−4); PD-L1; PD−1; TIM−3; lymphocyte-activation gene 3 (LAG−3); Gal−9; sCD27; programmed cell death-ligand 2 (PD-L2)] and C-reactive protein (CRP)	**CD27CD28 cells within the $CD8^+$ compartment terminally differentiated effector memory re-expressing CD45RA (TEMRA) $CD8^+$ subpopulation: the fraction of cells low amount of cells co-expressing CD27 and CD28 in subpopulation effector memory re-expressing CD45RA (TEMRA) $CD8^+$ higher proportion of cells lacking both costimulatory receptors high CD57, both in the total $CD8^+$ pool and in the TEMRA $CD8^+$ subpopulation high $CD3^+CD16^+$ cells (NK-like T cells) higher T-cell $p16^{INK4a}$ expression**
10 Zhang et al. (2023)	5106	Lung cancer, Digestive cancer, Colorectal cancer, others older than 65 years / 66.43 % having received surgery, 14.96 % having received radiotherapy, and 57.17 % patients having received chemotherapy.	FRAIL scale, and patients with≥ 3 positives out of a total of five components were assumed to be frail	neutrophil-to-lymphocyte ratio (NLR) NLR< 3 =no inflammation platelet-to-lymphocyte ratio (PLR), lymphocyte-C-reactive protein ratio (LCR) and albumin	**Increasing NLR PLR, high LCR, and clinical condition of hypoalbuminemia**
11 CORONA et al. (2013)	95	Breast Cancer, 70 years or older / at the moment of diagnosis before surgery or chemotherapy treatments	Fit, Unfit, and Frail according to the CGA criteria	Two different validated targeted metabolomics analytical platforms based on liquid chromatography tandem mass spectrometry 1.: serum profile of amino acids 2.:serum profile for acylcarnitines	**b-aminoisobutyric acid (bAib) and other non-proteinogenic amino acids such 3- methyl-hystidine (3MHis), hydroxyproline (Hyp), reduced serum concentration of Tryptophan (Trp) and Serine (Ser) Increase of C10 and C14 acylcarnitines**
12 Gilmore et al. (2020)	144	Breast Cancer Aged 50 and Over, stage I-III / Receiving Chemotherapy	modified Fried score consisting of four self-reported measures (weakness, exhaustion, physical activity, and walking speed; 0–4, 1 point for each)	Serum levels of interleukin (IL) 6, and soluble tumor necrosis factor-alpha (sTNFR) I and II	**High pre-chemotherapy serum levels of IL−6, sTNFRI, and sTNFRII**
13 Dalmasso et al. (2018)	89	Breast Cancer Stages: • Locally-advanced • Non-metastatic/ Inclusion/Pre-treatment (post-surgery and pre-chemo for chemo group) 3 months after inclusion or the day of last chemo for chemo group 1 year after inclusion	G8- Score and the Flemish version of the Triage Risk Screening Tool (fTRST) Bal- ducci Frailty score and Leuven Oncogeriatric Frailty Score (LOFS)	• miR−34a • miR−320b • miR−378a • miR−20a • miR−30b • miR−106b • miR−191 • miR−301a • miR−374a telomere length, IL−6, IL−10, TNF-α, RANTES, MCP−1, IGF−1	**• miR−34a • miR−320b • miR−378a • miR−20a • miR−30b • miR−106b • miR−191 • miR−301a • miR−374a**
14 Falandry et al. (2015)	109	Ovarian Cancer Stages: FIGO Stage III-IV / Pre-treatment	Geriatric Assesements: ADL: Activities of Daily Living; IADL: Instrumental Activities of Daily Living; BMI: Body Mass Index; ECOG: Eastern Cooperative Oncology Group; GDS: Geriatric Depression Scale; HADS: Hospital Anxiety and Depression Scale; MMS: Mini- Mental Scale	TL	**TL**
15 Gilmore et al. (2021)	1.634	Breast Cancer Stages: I-IIIC/ 581 Pre-chemotherapy 547 post-chemotherapy	modified Fried's score (0−4) using self-reported measures of weakness, exhaustion, walking speed, and physical activity	•Albumin•Hemoglobin •Hematocrit• Lymphocytes • LMR (lymphocyte monocyte ratio)• Monocytes• Neutrophils • NLR (neutrophil-to-lymphocyte	**Pre-chemotherapie:Total WBC, neutrophils, NLR Post-chemotherapie::Increase from pre-to-post chemo levels of total WBC, neutrophils, and NLR associated with post-**

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Table 1 (*continued*)

Reference	Cases (n)	Type of Tumor/ Therapy	Frailty instruments	Investigated biomarkers	**Biomarkers with significant correlation with frailty**
		506 six months post-chemotherapy		ratio)• Platelets• Total WBC (white blood cells)	**chemo frailty and in participants who received growth factors with chemo.**
16 Harneshaug et al. (2019)	255	Mixed Sample:• Breast longitudinal • Prostate• Other GI• Lung• Colorectal• OtherStages:• Localized• Locally-advanced• Metastatic/ Pre-treatment	modified GA (mGA). Eight different domains were assessed; comorbidity, activities of daily living (ADL), symptoms of depression, falls, polypharmacy, cognitive- and physical function, and nutritional status Balducci criteria	GPS (Glasgow prognostic score, combines valuesof C-reactive protein (CRP) and albumin, and is scored from 0 to 2 points, 0: low CRP/high albumin), 2: high CRP/ low albumin) IL−6 TNF-α	**higher GPS**
17 Lealdini et al. (2015)	52	Mixed Sample: Breast Prostate Stomach Colorectal Head and Neck Lung Endometrial Stages: Localized Metastasized / Pre-treatment	Edmonton Frailty Scale (EFS)	mGPS, (modified Glasgow Prognostic Score) (McMillan, 2013)	**High mGPS**

CAR: CRP/ albumin ratio; CRP: C-reactive protein; IGF: insulin-like growth factor; IFN: interferon; IL: interleukin; MCP: monocyte chemotactic protein; MMA: methylmalonic acid; PD: programmed cell death protein; PD-L: programmed death-ligand; TGF: transforming growth factor; TL: telomere length; TNF: tumor necrosis factor

with frailty included interleukin (IL)-6, IL-8, C-reactive protein (CRP), an increased CRP to albumin ratio (CAR), and the leukocyte count or the proportion of neutrophils (1, 3, 4, 5, 6, 8, 10, 12, 15, 16, 17) in Table 1). The most common significant finding in the included studies was the association of IL-6 with frailty, reported in five studies. Three studies showed significance with CRP, while one study showed significance with IL-8 (Buigues et al., 2020).

Additionally, three studies demonstrated a significant correlation with an elevated CRP to CAR (8, 16, 17 in Table 1).

Two studies reported a correlation between frailty and generally low leukocyte levels (1, 6 in Table 2). (Nishijima et al. (2017) and (Q. Zhang et al., 2023) described a correlation with a high neutrophil-to-lymphocyte ratio (NLR). Gilmore et al. (2020) reported an increase from pre- to post-chemotherapy levels of total white blood cells (WBC), neutrophils, and NLR associated with post-chemotherapy frailty.

One of the studies indicates that higher levels of methylmalonic acid

Table 2
Quality assessment - Newcastle-Ottawa Scale (NOS) – Table of results.

Studie	**Selection** Sum of points awarded for the selection process (up to 4 points)	**Comparability** Sum of the points for the comparability of the study groups (up to 2 points)	**Outcome/Exposure** Sum of points for the quality of the result/exposure measurement (up to 3 points)	**Total score**	**Details**
1 Navarro-Martínez et al. (2019)	3	2	3	8/9	Case-control study, good comparability, unclear study inclusion period
2 Wu et al. (2023)	3	2	3	8/9	Good comparability, unclear study inclusion period
3 Rønning et al. (2010)	4	2	3	9/9	
4 Brouwers et al. (2015)	4	2	2	8/9	
5 Nishijima et al. (2017)	4	2	3	9/9	
6 Buigues et al. (2020)	4	2	1	7/9	Good comparability, short follow-up period
7 Berben et al. (2021)	3	1	1	5/9	
8 Burgassi et al. (2021)	4	2	2	8/9	
9 Berben et al. (2020)	4	2	3	9/9	
10 Zhang et al. (2023)	4	2	3	9/9	
11 CORONA et al. (2013)	4	1	2	6/9	
12 Gilmore et al. (2020)	4	2	3	9/9	
13 Dalmasso et al. (2018)	4	2	1	7/9	
14 Falandry et al. (2015)	2	2	2	6/9	
15 Gilmore et al. (2021)	2	2	3	7/9	Poor comparability of selection (age, gender), clear study inclusion period
16 Harneshaug et al. (2019)	2	1	3	6/9	Various tumor entities
17 Lealdini et al. (2015)	2	2	3	7/9	Good selection and outcome assessment, short study inclusion period

(MMA) at the time of breast cancer diagnosis are associated with clinical frailty. Methylmalonic acid (MMA), a metabolite of propionate metabolism, exhibits an age-dependent increase and may act as a marker for frailty, aiding in the identification of patients at greater risk for worse treatment outcomes (Wu et al., 2023).

3.7. MicroRNA

In two studies (7, 13 in Table 1) microRNAs (miRNAs) were investigated as biomarkers for frailty in patients with breast cancer prior to treatment. Various assessment tools were used, including the Leuven Oncogeriatric Frailty Score, the Flemish Triage Risk Screening Tool, and G-8 geriatric screening tool. On the other hand, Dalmasso et al., (2018) showed that higher levels of miR-374a and lower levels of miR-320b were associated with reduced frailty in the Leuven Oncogeriatric Frailty Score (Dalmasso et al., 2018). Moreover, miR-301a values negatively correlated with frailty in the Flemish Triage Risk Screening Tool. Additionally, lower levels of miR-106b, miR-191, and miR-320b, along with higher levels of miR-374a, were identified as independent predictors for frailty accumulation based on G-8 geriatric screening tool-.

3.8. Immune cells: T-lymphocytes

Berben et al. discovered that T-cell populations, particularly CD8 + T-cells, exhibited significant age-related changes (Berben et al., 2021). Older patients showed reduced levels of CD8 + T-cells, indicating a weakened adaptive immune response associated with immunosenescence.

Furthermore, CD3 + T-cells and tumor-infiltrating lymphocytes (TILs) were highlighted. It was found that higher infiltration of CD3 + T-cells correlated with better immune responses in younger patients. In terms of tumor immune infiltrate, lower levels of stromal tumor-infiltrating lymphocytes (sTILs) were more common in older and frailer patients.

3.9. Telomere length

Two studies examined the relationship between telomere length and deficit accumulation frailty, using the Balducci system (Ferrat et al., 2017), Leuven Oncogeriatric Frailty Score, and the geriatric vulnerability score in the pre-treatment phase (4, 14 in Table 1). In patients with breast cancer, the results were not significant (Brouwers et al., 2015). However, in patients with ovarian cancer, shorter telomere length was associated with a geriatric vulnerability score of ≥ 3 (Falandry et al., 2015).

3.10. Risk of bias and quality assessment

According to the NOS, 4 articles had less than 7 out of a total of 9 possible points. 9 of the 14 studies, and thus the majority, showed a low risk of bias, which reflects the majority of the included studies (Table 2). Further details can be found in Appendix 2.

4. Discussion

The current literature encompasses only limited studies regarding biomarkers for frailty in patients with solid tumors. So far, IL-6, CRP and NLR were identified as promising biomarkers documented in at least two different studies (1,6 in Table 1).

Increased CRP levels have been consistently associated with greater frailty in cancer patients. For example, a meta-analysis by Nishijima et al. has highlighted that elevated CRP values served as an independent predictor for poor prognosis and a higher complication rate in patients with solid tumors (Nishijima et al., 2017).

IL-6 is a pro-inflammatory cytokine that has been associated with frailty, particularly in cancer and aging populations (Laino et al., 2020; Naqash et al., 2023). Elevated levels of IL-6 are linked to increased physical impairment and a higher susceptibility to treatment-related side effects, as it plays a role in muscle loss and inflammatory pathways contributing to frailty (Kojima et al., 2020). Furthermore, low levels of inflammatory markers like IL-6 and CRP have been shown to correlate with better survival in elderly adults living independently. This finding suggests that lower inflammation may contribute to improved prognosis, independent of other age-related and clinical factors (Xue et al., 2019). IL-8 however, showed inconsistent results as an indicator of frailty, potentially due to differences in the analytical methods employed and variability in sample sizes. Other cytokines, such as tumor necrosis factor-alpha (TNF-α), were also investigated but exhibited mixed associations that depended on tumor type and the timing of treatment. Research has shown that elevated inflammatory markers, including IL-6, NLR, CRP correlate with the severity of frailty, both before and during cancer treatment (Giovannini et al., 2011; Rønning et al., 2010). For instance, increased NLR has been found to be a significant predictor of frailty in patients with breast cancer (Gilmore et al., 2021). These changes in blood cell counts relate to the inflammatory responses triggered by cancer therapies. A systematic review by Sass et al. in 2023 further highlights the central role of inflammation in frailty among cancer patients, emphasizing the need for more studies to refine the use of inflammatory biomarkers in clinical practice. Our results are supported by the work of Sass et al. (2023). Although the inclusion criteria encompassed all solid tumor types, the research yielded particularly significant results for breast, prostate, and mixed solid tumors, as well as for ovarian and colorectal cancer.

The combination of CRP and albumin levels proved to be significantly associated with the accumulation of deficits of existing frailty, indicating the potential of this combination as a prognostic marker. Low serum albumin levels have been associated with poorer prognosis and increased frailty in cancer patients (Balducci and Extermann, 2000). A low albumin level often indicates malnutrition and catabolic processes contributing to frailty (Zhao et al., 2021). In three of the included studies, low albumin correlated with elevated CRP as a frailty indicator. In line with this, recent literature has also begun to explore frailty and biomarker integration within specific tumor types, such as cervical cancer. In their editorial, Golia D'Augè, Di Donato, and Giannini (2024) emphasize the clinical importance of frailty assessment and biomarker application in the individualized treatment of early-stage cervical cancer. They highlight that incorporating frailty parameters can guide therapeutic decisions, particularly in elderly or comorbid patients, and underscore the relevance of molecular and inflammatory biomarkers to optimize surgical planning and patient outcomes. These insights support the growing notion that frailty and biomarker profiling should be considered in disease-specific contexts to enhance precision medicine approaches in oncology (D'Oria et al., 2024).

Furthermore, epigenetic alterations and telomere length were examined, with some studies suggesting possible connections to frailty; however, the existing evidence remains inconsistent.

Furthermore, epigenetic alterations and telomere length were examined, with some studies suggesting possible connections to frailty; however, the existing evidence remains inconsistent. Telomere shortening and epigenetic changes, such as modifications in DNA methylation and miRNAs, have been implicated in frailty, including among cancer patients. Shortened telomeres can impair cell function and increase susceptibility to disease by promoting genomic instability. Similarly, age-related miRNA disturbances contribute to cellular aging, and their altered expression can be linked to frailty in cancer (Rupaimoole et al., 2016). However, research on biomarkers like telomere length and miRNAs in the context of solid tumors and frailty is still limited and requires further exploration (Barnes et al., 2023; C. Zhang et al., 2015; Zhou et al., 2018).

In contrast to blood biomarkers, saliva analysis offers a non-invasive method for assessing biomarkers associated with frailty. Saliva samples

may contain cytokines, hormones, and other metabolic markers that provide valuable information about the physiological state of patients. Saliva also contains inflammatory cytokines like IL-6 and TNF-α, which can be used as markers for systemic inflammation. A study by Sahibzada et al. demonstrated that high concentrations of IL-6 and TNF-α in saliva are correlated with worse clinical outcomes in cancer patients (Sahibzada et al., 2017). Studies have shown that specific salivary biomarkers, such as certain inflammatory cytokines and stress hormones, may correlate with frailty (Benito-Ramal et al., 2023; Noublanche et al., 2019). Saliva analysis could thus contribute to a better understanding of the systemic inflammation and stress that patients with solid tumors are exposed to. Despite this potential, no studies could be identified and included in our review that investigated salivary biomarkers in frail patients with solid tumors. Especially salivary-α-amylase brought significant correlations in the characterization of fragile patients for example in the study of Furtado et al. (Furtado et al., 2020). Decreased levels of salivary α-amylase were detected in the fragile subgroup, possibly reflecting the weakened immune barrier of fragile patients (Walsh et al., 2011). Advantages in the use of salivary biomarkers in clinical practice over serum markers are, in particular, that non-invasive, simple, low-cost sample collection is possible, which is of particular benefit to the fragile patient population (Niebla-Cárdenas et al., 2023; Yan et al., 2009).

Moreover, the combination of blood and salivary biomarkers could provide a more comprehensive perspective on frailty in patients with solid tumors. We focused our research on patients with solid tumors because evaluating general blood biomarkers in patients with hematologic malignancies would have been more challenging. This difficulty arises from potential biases related to their underlying conditions, which can complicate the analysis of these biomarkers. A major limitation across the included studies is the substantial heterogeneity in definitions and assessment tools for frailty, which impairs comparability and precludes meta-analyses. Moreover, limited data on salivary biomarkers restricts conclusions about their clinical potential, despite theoretical advantages such as non-invasiveness. Variability in tumor types, treatment stages, and follow-up durations also introduces potential bias. To improve future research, studies should adopt consistent frailty definitions and validated assessment instruments to enhance comparability. Given their practical benefits, targeted investigations into salivary biomarkers—such as inflammatory cytokines and stress hormones—in frail oncology patients are urgently needed. Increasing sample sizes and extending follow-up durations would further strengthen the understanding of associations between biomarkers, frailty progression, and treatment outcomes.

4.1. Strengths and weaknesses

To our knowledge, we present a comprehensive review on published data concerning blood and salivary biomarkers for frailty in solid tumors for the first time. However, it must be noted that the studies employed varying conceptual definitions of frailty and different instruments to measure it. Another bias to consider is the onset of frailty in solid tumors which may be multifactorial, influenced by factors such as the time since cancer diagnosis, treatments, and the specific biology of individual solid tumors. Furthermore, our study reanalyzed published data. The quality of collected data was all over good, the majority of the included studies showed a low risk of bias (Table 2). The existing risk included incomplete clinical data, the heterogeneity of the studies with regard to the biomarkers investigated, tumor types and frailty instruments. Due to the heterogeneity of the biomarkers and studies, a metanalysis could not be performed.

5. Conclusion

An elevated inflammatory status and corresponding increased inflammatory markers such as CRP and IL-6 in the blood are often significantly associated with frailty in patients with solid tumors. These markers could represent an opportunity to establish suitable biomarkers for frail cancer patients. Frailty biomarkers for solid tumors in saliva were not examined so far. Our findings indicate that the current literature employs varying conceptual definitions of frailty and different instruments to measure it.

Our results emphasize the need for further validation of frailty instruments, as well as clear conceptual and operational definitions of frailty in the field of oncology. Overall, the reports included in this review suggest that inflammatory pathways associated with the proliferation of immune cells at the time of diagnosis and treatment are linked to the development of frailty and its symptoms.

Future studies will benefit from a comprehensive set of biomarkers that are adjusted for cancer stages, time since diagnosis and treatment, and type of treatment. To date, the most promising markers are IL-6, CRP and NLR. Larger sample sizes and longer follow-up periods should also be considered. Further research is needed to establish suitable biomarkers for frailty in oncological patients, particularly in saliva, as a non-invasive, simple measurement.

Author Contribution

Conceptualization: VL, SH, LCO. Design: VL, SH. Data acquisition: VL, SH, LCO. Analysis and interpretation: SH, VL, WB. Writing- original draft of the manuscript: SH, VL. Writing - review and editing: SH, VL, LCO, WB, AH. All authors have read and agreed to the published version of the manuscript. All authors contributed to the article and approved the submitted version.

Ethical approval

This is a systematic review of the literature and no ethical approval is required.

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Declaration of Competing Interest

The authors state that no relevant conflicts of interests are to declare.

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Appendix

Appendix 1: Literature search strategy

Appendix 2: Newcastle-Ottawa-Scale (NOS) Ottawa Hospital Research Institute. (n.d.). *The Oxford 2011 Levels of Evidence*. Ottawa Hospital Research Institute. https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.critrevonc.2025.104939.

Data availability

All data generated or analyzed during this study are included in this

article and its tables and figures. Further enquiries can be directed to the corresponding author.

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