Systematic Review

Cytokine Expression in Cancer Survivors Suffering From Chronic Pain: A Systematic Review

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Background: Chronic cancer-related pain remains underdiagnosed and undertreated, although it affects 40% of cancer survivors. Recent insights suggest that cytokine signaling between immune, neuro, and glial cells contributes to chronic pain.

Objectives: This study systematically reviewed cytokine levels and their relation to chronic cancer-related pain and, additionally, investigated differences in cytokine levels between cancer survivors with and without chronic pain.

Study Design: Systematic review.

Methods: This systematic review was conducted and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines (PRISMA). The study conducted a systematic literature search in the databases PubMed, Web of Science, and Embase for articles examining cytokine levels and pain experience at a time point of a minimum of 3 months post-cancer diagnosis. Pain experience was categorized into a total pain score, pain intensity, and pain interference. The risk of bias was assessed using the Newcastle Ottawa Scale.

Results: Eight articles were included, investigating 6 cancer types and 30 cytokines. Moderate evidence was found for pro-inflammatory cytokine IL-6 to be correlated with pain intensity, of which higher levels are observed in cancer survivors experiencing chronic pain compared to pain-free survivors. Moderate evidence was found for TNF-α to be not correlated with any pain experience, which is similar for anti-inflammatory cytokines IL-8 and IL-10 with pain intensity. For the remaining 26 cytokines and pain outcomes, only limited evidence was found for an association or alteration.

Limitations: The number of included studies was small. Overall, studies showed a moderate risk of bias, except one indicated a high risk of bias.

Conclusion: More standardized post-cancer treatment studies are warranted to confirm these results and explore associations and alterations of other cytokines. Nonetheless, moderate evidence suggests that elevated levels of IL-6, in contrast with TNF-α levels, are correlated with pain intensity in cancer survivors experiencing chronic pain compared to pain-free survivors.

Key words: Cytokines, interleukin, chronic cancer-related pain, chronic pain, persistent pain, cancer pain, IL-6, TNF-α

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Quality of life (QoL) is one of the most concerning health issues for cancer survivors, with chronic pain and fatigue proposed to play a major role (1,2). Research to improve the QoL gained more importance due to better cancer treatment options and, consequently, more cancer survivors (2). Nevertheless, chronic pain following cancer treatment remains underdiagnosed and undertreated (2-4).

Cancer-related pain can be classified according to the International Classification of Diseases (ICD-11) into 2 different categories based on time perception or etiology. The first category distinguishes acute from chronic pain; acute pain is experienced within a few seconds to less than 3 months, and chronic pain lasts longer than 3 months (1). Although experiencing acute pain after an invasive treatment such as surgery is normal, it is remarkable that some cancer survivors continue to experience pain for an extended period of time (5-7). The second category distinguishes pain based on etiology; pain could be caused by the tumor itself (e.g., growth, metastasis) or induced by treatment-related tissue or nerve damage (1).

In the literature, it is described that almost every cancer treatment possibly causes chronic pain (1). Pain commonly described in cancer survivors is either chemotherapy-induced peripheral neuropathy (CIPN) or chronic postoperative pain. CIPN is induced by typical chemotherapeutic agents such as taxanes (e.g., paclitaxel) and platinum-based drugs (e.g., oxaliplatin). Besides, radiation-induced neuropathy due to fibrosis and arthralgia caused by aromatase inhibitors are also painful side effects (8-10). The second type, chronic postoperative pain, is particularly common after radical surgeries such as mastectomy in breast cancer patients and thoracotomy in lung cancer patients (1). Remarkably, despite these facts, little is known about the mechanism of pain chronification due to cancer treatment, which describes the process of acute pain evolving into chronic pain, even though it affects up to 40% of cancer survivors (1,11,12).

Recent insights suggest the involvement of the immune system in the development and maintenance of chronic pain (13). More specifically, the pro-inflammatory cytokine signaling between immune, neuro, and glial cells appears to play an essential role (4,14,15). Whenever tissue damage or a nerve injury takes place, various pathogen- and damaged-associated molecular patterns are exposed to the environment, where they are recognized by their corresponding receptor. Subsequentially, immune cells are recruited towards the invasion site to secrete pro-inflammatory cytokines, aiding both B- and T-cells (14). Positive feedback loops amplify this immune response, whereas the release of anti-inflammatory cytokines counteracts this to maintain homeostasis (14,15). Disturbed cytokine expression has also been described in animals suffering from CIPN, supporting the evidence for dysregulation of the cytokine balance in response to cancer treatment (16-19).

Furthermore, the release of inflammatory mediators can induce changes in the properties of the peripheral nociceptors and the chemical environment, enhancing peripheral sensitization (20-22). Besides, it is supposed that these neuroinflammatory changes are also at the root of enhanced central sensitization (22,23). Moreover, prolonged enhanced sensitization can form new connections between neurons, whereby a normal signal can be misinterpreted as pain (24). As such, nociplastic pain, "pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain" (22), can develop and explain the persistence of pain beyond the acute phase. Altered inflammation may thus cause hypersensitivity or prolonged sensitivity, supporting the maintenance of cancer-related chronic pain.

A better understanding of chronic pain following cancer treatment and the contributing role of the immune system would allow us to gain more insight into the underlying mechanism(s) of pain chronification. Therefore, this systematic review aims to summarize the literature on cytokine expression and its relation to pain in cancer survivors suffering from chronic pain after undergoing anti-neoplastic treatments. Hereby, the following 2 questions will be addressed: first, what is the relation between cytokine expression and chronic pain in cancer survivors? Second, what is the difference in cytokine expression comparing cancer survivors with and without chronic pain?

Methods

This systematic review was reported according to the Preferred Reporting Items for Systematic Reviews (PRISMA) statement (25). The protocol was registered at the International Prospective Register of Systematic Reviews (Prospero: RD42022296924).

Search Strategy

A systematic literature search was developed and conducted by the author ADG based on the Popula-

tion, Intervention, Comparison, and Outcome (PICO) framework in the following 3 databases: PubMed, Web of Science, and Embase. The original search was conducted between 2 and 17 December 2021 and updated on January 16, 2023. The detailed search strategy is presented in Appendix 1.

Eligibility Criteria

Studies were included if they reported on cancer survivors following the definition by the National Cancer Institute: " A person is considered a survivor from the time of cancer diagnosis until the end of life." More specifically, adults (≥ 18 years old) diagnosed with cancer and undergoing or finished any cancer treatment (e.g., surgery, radiation therapy, chemotherapy) were eligible. Chronic pain could be assessed by self-reported questionnaires or interviews, while cytokine levels were assessed in blood plasma or serum. Both assessments were required to be measured at the same time, at least 3 months post-diagnosis. Additional inclusion criteria were: the article had to report original research, was available in full text, written in English, Dutch, French, or German, and published since 2000.

Studies were excluded if survivors had a medical condition that could alter cytokine levels (e.g., autoimmune diseases) or did not report chronic pain (i.e., measurement before 3 months post-diagnosis). Animal studies, case reports, and secondary research were other reasons for exclusion.

Study Selection

The retrieved records were imported into Covidence (www.covidence.org) for screening and data extraction. All studies were independently screened against the abovementioned eligibility criteria by 2 reviewers (ADG and TVV) in 2 stages. First, articles were screened against eligibility criteria based on title and abstract. Secondly, articles were screened based on full text. Reviewers were blinded to each other's decisions until the completion of screening. In case of disagreement, a consensus meeting took place where the 2 reviewers made a final decision. A third reviewer was consulted (MM) if a consensus was not reached. Records that did not meet eligibility criteria were excluded. In addition to the searched databases, a hand search of the reference lists of the eligible records for data extraction was performed in 2 stages, as mentioned above.

Data Collection

Two reviewers (ADG and TVV) independently extracted data which was systematically summarized in an evidence table (Table 1). The presented data include: (i) general information (i.e., author, publication date, country of the study, study design), (ii) demographics of the participants (i.e., sample size, gender, cancer type, cancer treatment, age), (iii) pain related variables (i.e., time of pain assessment, assessment methodology, pain outcome), (iv) cytokine related variables (i.e., time of assessment(s), assessment methodology, cytokines), and (v) results on the relationship between pain and cytokine expression and/or comparison between cancer survivors with and without chronic pain. If essential data was lacking, corresponding authors were contacted by email and requested to provide the missing data.

Risk of Bias Assessment

Newcastle Ottawa Scale

The risk of bias (RoB) in the included observational studies was assessed using the Newcastle Ottawa Scale (NOS) adapted for the used study design (26). The NOS evaluates studies on 3 categories of bias according to the following criteria: (i) selection bias (4 items), (ii) comparability bias (1 item), and (iii) exposure or outcome bias (3 items or 2 items for cross-sectional studies). Each item was awarded a star in case of low risk of bias, except for the subcategory comparability bias, where 2 stars could be awarded (very low risk of bias). In cross-sectional studies, 2 stars could be awarded for both items, 'ascertainment of exposure' and 'assessment of the outcome.' Consequently, the total NOS score for case-control and cohort studies ranged from 0-9 stars, whereas the NOS score for cross-sectional studies varied from 0-10 stars. Two independent researchers (ADG and TVV) assessed the risk of bias in the included studies. In case of disagreement, a consensus decision was made by the 2 reviewers, or a third party (MM) was consulted in case of disagreement.

Level of Evidence

A level of evidence between A1 (at least 2 independently conducted studies of evidence level A2) and D (expert level) was allocated for each included article (27). Both study design and RoB were taken into account following the EBRO-guidelines of the Dutch Institute for Healthcare Improvement (27). Then, a level of conclusion (LoC) was assigned, taking the level of evidence and the consistency of the results into account (27).

Table 1. *Characteristics of included studies and summary of findings table.*

Publication	Demographics	Assessments			
Author Year Country Study Design	**Population Sample size (n) Treatment(s) Gender (M/F) Age (mean ± SD years)**	**Time assessment of both outcomes Statistical analysis**	**Pain assessment**	**Cytokine assessment**	**Results[a]**
Addison et al (2014) Canada Cohort study	Breast cancer patients with bone metastasis (n = 63) History of min. 3 months of 3-4 weekly bisphosphonate therapy F (100%) Age: NR	Correlation at Baseline[b]	BPI (NRS 0-20): Pain intensity (NRS 0-10) Pain interference (NRS 0-10) FACT-BP (NRS 0-60): Pain interference	ELISA: Serum TGF-β	Relationships between Pain intensity & TGF-β: BPI ($\rho = 0.12$, $P > 0.05$) Pain interference & TGF-β: BPI ($\rho = 0.03$, $P > 0.05$) FACT-BP ($\rho = 0.00$, $P > 0.05$)
Fazzari et al (2020) Canada Cohort study	Breast cancer patients with bone metastasis (n = 57) History of min. 3 months of 3-4 weekly bisphosphonate therapy F (100%) Age: NR	Correlation and regression independent of patient number and time points baselineb, W12, W24, W36, W48	BPI (NRS 0-20): Total pain score	HDHSTC14: Serum IL-1β, IL-2, IL-4 , IL-5, IL-6, IL-8, IL-10, IL-12, IL-13, IL-17A, IL-23, TNF-α, IFN-γ, GM-CSF	Relationship between Total pain score & cytokines: **IL-1β ($r = -0.2188$, $R^2 = 0.055199$, $P = 0.0091$)** **IL-2 ($r = -0.2792$, $R^2 = 0.078$, $P = 0.00008$)** **IL-4 ($r = -0.2641$, $R^2 = 0.06977$, $P = 0.0016$)** **IL-5 ($r = -0.2114$, $R^2 = 0.044688$, $P = 0.0119$)** IL-6 ($r = -0.06383$, $R^2 = 0.004074$, $P = 0.4521$) IL-8 ($r = 0.1459$, $R^2 = 0.002575$, $P = 0.5501$) IL-10 ($r = -0.009846$, $R^2 = 0.000097$, $P = 0.9077$) **IL-12 ($r = -0.2248$, $R^2 = 0.050546$, $P = 0.0074$)** IL-13 ($r = -0.1392$, $R^2 = 0.019378$, $P = 0.0997$) **IL-17A ($r = -0.2722$, $R^2 = 0.0741$, $P = 0.0011$)** **IL-23 ($r = -0.1841$, $R^2 = 0.033911$, $P = 0.0288$)** TNF-α ($r = 0.09002$, $R^2 = 0.008103$, $P = 0.2885$) **IFN-γ ($r = 0.2551$, $R^2 = 0.065075$, $P = 0.023$)** **GM-CSF ($r = -0.2349$, $R^2 = 0.055199$, $P = 0.005$)** Stepwise regression with sign. univariate correlations: **$R^2 = 0.2014$** with GM-CSF, IFN-γ, IL-1β, IL-2, IL-4, IL-5, IL-12(p70), IL-17A and IL-23 in the final multivariable model
Starkweather (2010) US Case-control study	Breast cancer, grade II -III (n = 40) Systemic adjuvant cancer therapy; combination chemotherapy (100%) F (100%) Pain group (CIPN): n = 20 Age: $\bar{x} = 56.8 \pm 6.6$ No pain group: n = 20 Age: $\bar{x} = 53.4 \pm 5.6$	Correlation and comparison between 6 and 12 months post-diagnosis, completed cancer therapy	Sensory & motor exam: Grade CIPN MPQ-SF (NRS 0-45): Total pain score SF-36 bodily pain subscale (NRS 0-6): Total pain score	Quantikine High Sensitivity Immunoassay kits: Serum IL-6	Relationship between Total pain score & IL-6: **MPQ-SF ($r = 0.519$, $P < 0.01$)** **SF-36 ($r = -0.815$, $P < 0.01$)** Comparison of IL-6 between Pain vs no pain: **Pain > no pain ($P < 0.001$)**

Table 1 cont. *Characteristics of included studies and summary of findings table.*

Publication	Demographics	Assessments			Results[a]
Author Year Country Study Design	**Population Sample size (n) Treatment(s) Gender (M/F) Age (mean ± SD years)**	**Time assessment of both outcomes Statistical analysis**	**Pain assessment**	**Cytokine assessment**	
Boland et al (2013) UK Cross-sectional study	Multiple Myeloma (n =32) History of Hematopoietic Stem Cell Transplantation & Chemotherapy: Thalidomide and/or lenalidomide (81%) Vincristine (84%) Bortezomib (69%) Doxorubicin (66%) M/F : 17/15 Age: $\bar{x}$ = 61, (range 41-71)	Correlation at $\bar{x}$ = 5.5 years, range 2-12 years post-diagnosis	BPI-SF (NRS 0-20): Pain intensity (NRS 0-10) Pain interference (NRS 0-10) EORTC QLQ-C30 subscale pain (NRS 0-6): Total pain score	ECLIA: Serum IL-6 EIA: Serum TNF-α	Relationship between: Pain intensity & cytokines: **IL-6 (ρ = 0.38, *P* = 0.03)** TNF-α (ρ = 0.27, *P* = 0.15) Pain interference & cytokines: **IL-6 (ρ = 0.52, *P* = 0.003)** TNF-α (ρ = 0.14, *P* = 0.46) Total pain score & cytokines: **IL-6 (ρ = 0.41, *P* = 0.02)** TNF-α (ρ = 0.04, *P* = 0.84)
Yehia et al (2019) Africa RCT	Colorectal cancer (n = 61) Chemotherapy: FOLFOX-6 (= 3 months) (100%) Arm A: no additional intervention (n = 31) 13M/18F Age: $\bar{x}$ = 45.9 ± 8.6 Arm B: additional daily oral L-carnosine (500 mg) (n = 30) 16M/14F Age: $\bar{x}$ = 45.6 ± 10.5	Association post-chemotherapy	NCI-CTCAE-V4: Grade neuropathy (0-2)	ELISA: Serum TNF-α	Relationship between neuropathy grading and TNF-α using ANOVA testing Arm A: Grade 0 (n = 1): $\bar{x}$ = 0.040 SD, *P* > 0.05 Grade 1 (n = 11): $\bar{x}$ = 0.034 ± 0.006 SD, *P* > 0.05 Grade 2 (n = 19): $\bar{x}$ = 0.031 ± 0.008 SD, *P* > 0.05 Arm B: Grade 0 (n = 12): $\bar{x}$ = 0.02 ± 0.007 SD, *P* > 0.05 Grade 1 (n = 17): $\bar{x}$ = 0.02 ± 0.007 SD, *P* > 0.05 **Grade 2 (n = 1): $\bar{x}$ = 0.04, *P* < 0.03**
Al-Mazidi et al (2018) Asia Case-control study	Prostate cancer with metastasis (n = 30) M (100%) Chemotherapy (100%): 3 cylces of Docetaxel/ Taxodere Pain group (NRS ≥ 3): n = 20 Age: $\bar{x}$ = 69 ± 2 (SEM) No pain group (NRS = 0): n = 10 Age: $\bar{x}$ = 71 ± 2 (SEM)	Regression and comparison at 1 month post-chemotherapy	NRS (0-10): Pain intensity	Luminex assay: Plasma IL-1α, IL-1β, IL-1, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12, IL-13, IL-15, IL-17, TNF-α, IFN-γ, CCL3, CCL4, CCL5, G-CSF, GM-CSF, Eotaxin, FGF, IP-10, MCP-1, PDGF-bb, VEGF,	Relationship between Pain intensity & cytokines : **IL-6 (R^2 = 0.28, *P* = 0.024)** Other 26 cytokines *P* > 0.05 Comparison of cytokines between pain vs no pain: Pain > no pain **IL-6 (*P* < 0.05)** **IL-8 (*P* < 0.05)** **IL-15 (*P* < 0.05)** **CCL4 (*P* < 0.05)** **CCL5 (*P* < 0.05)** **IP-10 (*P* < 0.05)** **VEGF (*P* < 0.05)**

Table 1 cont. *Characteristics of included studies and summary of findings table.*

Publication	Demographics	Assessments			Results[a]
Author Year Country Study Design	**Population Sample size (n) Treatment(s) Gender (M/F) Age (mean ± SD years)**	**Time assessment of both outcomes Statistical analysis**	**Pain assessment**	**Cytokine assessment**	
Dalton et al (2015) US Cohort study	Lung cancer patients (n = 12) with metastasis (n = 6, 50%) M/F: 4/8 Age: range 42-78	Comparison z-scores at 6 months post-diagnosis	BPI (0-20): Pain intensity (NRS 0-10) Pain interference (NRS 0-10)	ELISA: Plasma IL-6	Comparison between low pain (NRS ≤ 3) vs high pain (NRS ≥ 3) Pain intensity & IL-6: High pain (n = 6) > low pain (n = 6) (median z-score = NR) Pain interference & IL-6: High pain (n = 6) > low pain (n = 6) (median z-score = NR)
Honerlaw et al (2016) US Cohort study	Endometrial cancer (n = 71) Surgery (100%) Adjuvant therapy (94.1%): Chemotherapy (n = 20) Vaginal brachytherapy (n = 17) Whole pelvic radiation (n = 9) None (n = 35) F (100%) Age: $\bar{x}$ = 61 ± 9.1	Regression models at 4 months post-surgery	BPI (0-20): Pain intensity (NRS 0-10) Pain interference (NRS 0-10)	ECLIA: Plasma IL-1β, IL-6, IL-8, IL-10, IL-12, TNF-α, IFN-γ,	Mixed-effects linear regression models (across time points) with time since surgery, age, disease stage, surgical procedure, adjuvant therapy, and BMI as covariates: Pain intensity & cytokines: **IL-6 (β = 0.349, z = 2.43, *P* = 0.015)** IL-8 (β = 0.043, z = 0.27, *P* = 0.786) IL-10 (β = 0.058, z = 0.31, *P* = 0.753) TNF-α (β = 0.069, z = 0.30, *P* = 0.763) Pain interference & cytokines: IL-6 (β = 0.310, z = 1.49, *P* = 0.135) IL-8 (β = -.050, z = -0.22, *P* = 0.823,) IL-10 (β = -0.268 z = -1.06, *P* = 0.289) TNF-α (β = 0.030, z = 0.11, *P* = 0.916) Fixed-effects linear regression models (across time points) with time since surgery as covariate Pain intensity & cytokines: **IL-6 + (β = 0.387, t = 2.45, *P* = 0.017)** IL-8 (β = -0.038, t = -0.21, *P* = 0.831) IL-10 (β = 0.202, t = 0.96, *P* = 0.341,) TNF-α (β = -0.022, t = -0.07, *P* = 0.946) Pain interference & cytokines: IL-6 (β = 0.467, t = 1.95, *P* = 0.055) IL-8 (β = -0.224, t = -0.85, *P* = 0.399) IL-10 (β = -0.098, t = -0.31, *P* = 0.759) TNF-α (β = -0.278, t = -0.55, *P* = 0.581) Non-detectable cytokines IL-1β, IL-12, IFN-γ

a Only cytokines reported in the results section of the referred articles are reported.
b Baseline = history of 3 months of bisphosphonate therapy and before extension of the treatment.
Abbreviations: F = female, M = male, NR = not reported, Y/O= Years old, $\bar{x}$ = Mean, SD = standard deviation, SEM = Standard Error of Mean, BPI = Brief Pain Inventory, FACT-BP = Functional Assessment of Cancer Therapy-Bone Pain, SF-36 = Medical Outcomes Short-Form version 2, NRS = Numeric Rating Scale, BPI-SF = Brief Pain Inventory-Short Form, EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30, NCI-CTCAE = National Cancer Institute common Terminology criteria for Adverse Events, MPQ-SF = Short From McGill Pain Questionnaire, HSCT = Hematopoietic stem cell transplantation, ELISA = Enzyme-Linked Immune Sorbent Assay, ECLIA = Electrochemiluminescence immunoassay, EIA = Enzyme immunoassay, HDHSTC14 = Human High Sensitivity T-Cell Discovery Array 14-plex, TGF = Tumor growth factor, ρ = Spearman correlation coefficient, r = Pearson correlation coefficient, IL = Interleukin, MIP-1α = Macrophage inflammatory protein-1α,TNF = Tumor necrosis factor, VEGF = vascular endothelial growth factor, IP-10 = interferon- γ-inducible protein 10, CCL = Chemokine ligand, GM-CSF = Granulocyt-macrophage colony-stimulating factor, IFN = Interferon.
Significant values are indicated in bold.

Data Synthesis and Methods for Analysis

To outline the relationship and alterations between pain and cytokine results, a systematic narrative synthesis is given, with the information presented and summarized in text. If possible, the included studies were summarized per cytokine outcome concerning its associated pain outcome, namely pain intensity, pain interference, and/or total pain. Additionally, comparisons between cancer survivors with and without chronic pain were summarized per cytokine outcome.

Results

Study Selection

The final search strategy of January 2023 in the 3 databases yielded 3899 articles. After deduplication and screening on title and abstract as well as on full text, a total of 6 articles remained for the narrative synthesis (28-33). The study selection process is shown in Fig. 1. A hand search of the eligible articles' reference list resulted in 2 additional articles (34,35). The main reasons for excluding articles were a wrong outcome, followed by wrong study design, and wrong population.

Study Characteristics

Demographics

Key data of the 8 included articles are displayed in Table 1. All articles investigated the relationship between pain and cytokine levels or compared cytokine levels between cancer survivors with and without chronic pain. The overall sample size accounts for 321 cancer survivors, representing 6 different types of cancer: breast cancer (n = 3) (31,34,35), multiple myeloma (n = 1) (29), colorectal cancer (n = 1) (33), lung cancer (n = 1) (30), endometrial cancer (n = 1) (32) and, prostate cancer (n = 1) (28). Four of them reported the presence of metastasis (28,30,31,34). Overall, studies included cancer survivors treated with chemotherapy (n = 5) (28,29,32,33,35) or surgery (n = 2) (32,35) alone or in combination. In addition, bisphosphonate treatment (n = 2) (31,34), hematopoietic stem cell transplantation (n = 1) (29), and experimental treatments (n = 1) (33) such as L-carnosine were also reported.

Pain Assessment

In general, a total pain score, pain intensity, as well as pain interference were assessed using questionnaires or a physical examination. Most frequently, the Brief Pain Inventory (BPI) was used to assess both pain intensity and interference (n = 5) (29-32,34). However, one of these 4 articles (31) reported the combined BPI scores, whereas the other 3 distinguished between the pain intensity and pain interference scores. In addition to the BPI, the Functional Assessment of Cancer Therapy-Bone Pain (FACT-BP) (n = 1) (34) and the Numeric Rating Scale (NRS) (n = 1) (28) were also used to assess pain intensity. Besides, the following 3 questionnaires were used to assess the total pain score: (i) the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) (n = 1) (29), (ii) Short-Form McGill Pain Questionnaire (MPQ-SF) (n = 1) (35) and (iii) Medical Outcomes Short-Form version 2 (SF-36) (n = 1) (35). Lastly, both the National Cancer Institute (35) common Terminology criteria for Adverse Events (NCI-CTCAE.V4) (n = 1) (33), as well as a physical examination (n = 1) (35), evaluated the grade of neuropathy.

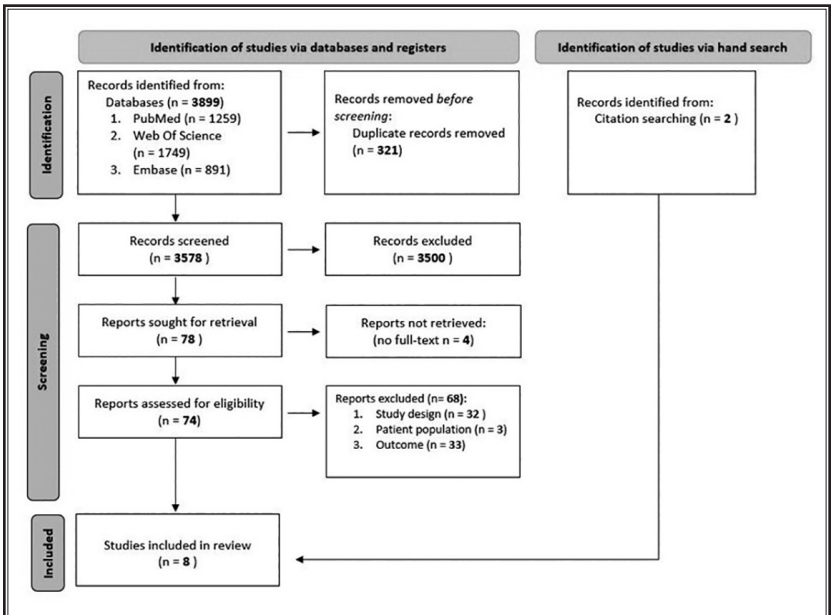

Fig. 1. *PRISMA flow diagram of the study selection process, adapted from (25).*

Cytokine Assessment

Only 3 of the included articles reported the withdrawal of the blood sampling in the morning, and the participants were sober in 2 of these 3 studies (30,31,34). Plasma (n = 3) (28,30,32) or serum (n = 5) (29,31,33-35) was extracted to assess cytokine levels using different techniques: Enzyme-Linked Immune Sorbent Assay (n = 3) (30,33,34), Luminex Assay (n = 1) (28), Electrochemiluminescence immunoassay (n = 2) (29,32), Enzyme immunoassay (n = 1) (29), Human High Sensitivity T-cell Discovery Array 14-plex (n = 1) (31) and Quantikine High Sensitivity Immunoassay kits (n = 1) (35). In 3 studies, the assessment of cytokine levels was performed in duplicate (30,32,34) or triplicate (n = 1) (35); the other studies did not mention this information. A total of 30 cytokines were evaluated: IL-1α (n = 1), IL-1β (n = 3), IL-1 (n = 1), IL-2 (n = 1), IL-4 (n = 2), IL-5 (n = 2), IL-6 (n = 6), IL-7 (n = 1), IL-8 (n = 3), IL-9 (n = 1), IL-10 (n = 3), IL-12 (n = 3), IL-13 (n = 2), IL-15 (n = 1), IL-17 (n = 2), IL-23 (n = 1), TNF-α (n = 5), IFN-γ (n = 3), CCL3 (n = 1), CCL4 (n = 1), CCL5 (n = 1), G-CSF (n = 1), GM-CSF (n = 2), Eotaxin (n = 1), FGF (n = 1), IP-10 (n = 1), MCP-1 (n = 1), PDGF-bb (n = 1), VEGF (n = 1) and TGF-β (n = 1).

Timing of Assessment and Method of Association

Both pain experience and cytokine levels were assessed at the same time. The earliest described time point was post-chemotherapy (33) or after 3 months of bisphosphonate treatment (31,34). The latest mentioned time point was 12 years post-diagnosis (29). In general, the assessments took place within the first year of cancer diagnosis but after completion of treatment (28,32,35).

To investigate the relationship between cytokine levels and pain experience, both correlations and regression analyses were conducted. Spearman correlations were calculated in 2 studies (29,34), and regression analyses were performed in 3 studies. Three articles performed a linear regression analysis, more specifically a univariate (31), mixed-effects (32), or fixed-effects linear regression model (32) in which the last 2 took covariates, such as age or time since surgery, into account. The study of Fazzari et al used a stepwise regression analysis (31).

Three studies explored differences in cancer survivors with pain compared to pain-free survivors using independent t tests (35), standardized z-scores (36), or the Kruskal Wallis test followed by Dunn's multiple comparisons (28). The study of Yehia et al (33) investigated alterations of cytokines levels in comparing different grades of neuropathy using ANOVA.

Risk of Bias and Level of Evidence

The RoB and level of evidence for the included studies are displayed in Tables 2 and 3. An agreement of 75% between both assessors was established before the consensus meeting. After the interrater comparison, a consensus was reached for all items. Overall, the included studies showed a moderate risk of bias, except for one study which showed a high risk of bias. Cross-sectional studies (29,30,33,34) lost most points due to unsatisfactory responders – non-responders rate, lack of comparability, self-reported pain questionnaires, and insufficient reporting of statistical measurements. Both case-control (28,35) and cohort studies (31,32) lost most points in the selection bias. Additionally, due to the usage of self-reports, no stars were awarded for the items 'ascertainment of exposure' or 'assessment of outcome' in the exposure/outcome bias. Studies were assigned a level of evidence depending on the study design of the extracted data; for example, the data of the included RCT had a cross-sectional study design (33). Case-control and cohort articles were assigned a level of evidence B (28,31,32,35), whereas non-comparative cross-sectional articles were assigned a level of evidence C (29,30,33,34).

Synthesis of Results

IL-6

Relationship With Chronic Pain

IL-6 levels were assessed in 5 studies, examining breast cancer (31,35), multiple myeloma (29), endometrial cancer (32), or prostate cancer (28). Three studies assessed total pain scores, showing conflicting results: on one hand, combined BPI scores were used in a simple univariate regression model independent of time points, and blood was collected in the morning while participants were sober, leading to non-significant results (31). On the other hand, the subscale of the EORTC QLQ-30 showed a moderate correlation with IL-6, while the MPQ-SF and SF-36 bodily pain showed a strong correlation (29,35). Here, both studies mentioned the completion of cancer treatment; however, the moment of blood collection was not reported. Furthermore, 3 of 5 studies assessed pain intensity and found evidence for an association with IL-6 levels in a timeframe of one-month post-treatment until 12 years post-diagnosis (28,29,32). Of these articles, 2 used the BPI (29,32) and one the NRS (28). Lastly, both Boland et al (29) and Honerlaw et al (32) also

Table 2. *Risk of bias and level of evidence of included cross-sectional studies.*

Cross-sectional	Selection				Comparability	Exposure/outcome		Total	LoE
Addison et al	*	*	-	**	-	*	-	Moderate	C
Boland et al	*	*	-	**	-	*	*	Moderate	C
Dalton et al	-	*	-	*	-	*	-	High	C
Yehia et al	*	*	-	**	-	*	-	Moderate	C

Table 3. *Risk of bias and level of evidence of included cohort/case-control studies.*

Cohort/case control	Selection				Comparability	Exposure/outcome			Total	LoE
Al-Mazidi et al	-	*	-	*	**	-	*	*	Moderate	B
Fazarri et al	*	*	-	-	-	-	*	*	Moderate	B
Honerlaw et al	*	*	-	-	**	-	*	-	Moderate	B
Starkweather	-	*	-	*	**	-	*	*	Moderate	B

assessed pain interference, reporting inconclusive results. The first demonstrated a moderate positive correlation in multiple myeloma cancer survivors who received chemotherapy, whereas the latter reported no association between IL-6 and pain interference in endometrial cancer survivors who underwent surgery (29,32).

There is inconclusive evidence for a relationship between IL-6 and total pain scores or pain interference (LoC 3). Moderate evidence indicates IL-6 levels are correlated with pain intensity (LoC 2).

Comparison Between Pain and Pain-Free Cancer Survivors

Two studies examined the difference in IL-6 levels between cancer survivors with or without chronic pain (28,35). Both studies demonstrated significantly higher IL-6 levels post-cancer treatment in cancer survivors experiencing chronic pain compared to pain-free survivors. In addition, the study of Dalton et al (30) compared cancer survivors experiencing high pain with low pain and showed higher IL-6 levels for both pain intensity as well as for pain interference. However, this study only reported z-scores to distinguish cancer survivors with high pain from low pain and did not report statistical calculations (30).

Moderate evidence indicates elevated IL-6 levels in cancer survivors experiencing chronic pain compared to the same cancer population not experiencing pain (LoC 2).

TNF-α

Relationship With Chronic Pain

TNF-α levels were assessed in the 5 included studies of which each one investigated a different cancer population i.e., breast cancer, multiple myeloma, colorectal cancer, prostate and endometrial cancer (28,29,31-33). Overall, no significant relationships were found for TNF-α and total pain scores (n = 2), pain intensity (n = 4), or pain interference (n = 2). Except for the study of Yehia et al (33), significantly higher TNF-α levels were reported only for the group neuropathy grade 2 who received FOLFOX-6 treatment with L-carnosine.

Moderate evidence indicates there is no relationship between TNF-α levels and total pain scores, pain intensity, or pain interference (LoC 2).

Comparison Between Pain and Pain-Free Cancer Survivors

Only one study compared TNF-α levels between cancer survivors with and without pain. No significant changes were reported between the compared groups (28).

Limited evidence indicates no alterations in TNF-α levels among cancer survivors experiencing chronic pain compared to the same cancer population not experiencing pain (LoC 3).

IL-8

Relationship With Chronic Pain and Comparison Between Pain and Pain-Free Cancer Survivors

Three articles studied IL-8 levels in breast cancer, prostate cancer, and endometrial cancer (28,31,32). No significant relationships were found for both cytokines and total pain scores (n = 1), pain intensity (n = 2), or pain interference (n = 1). Surprisingly, significantly elevated IL-8 levels were reported one-month post-

chemotherapy in prostate cancer survivors experiencing pain compared to pain-free survivors (28).

Limited evidence indicates no alterations in IL-8 for total pain scores or pain interference (LoC 3). Moderate evidence indicates no alterations in neither IL-8 levels for pain intensity (LoC 2).

Limited evidence indicates elevated IL-8 levels in cancer survivors experiencing chronic pain compared to the same cancer population without experiencing pain (LoC 3).

IL-10

Relationship With Chronic Pain and Comparison Between Pain and Pain-Free Cancer Survivors

Three articles studied both IL-10 levels in breast cancer, prostate cancer, and endometrial cancer (28,31,32). No significant relationships were found for both cytokines and total pain scores (n = 1), pain intensity (n = 2), or pain interference (n = 1). Also, no significant alterations were found for IL-10 levels when comparing prostate cancer survivors with and without chronic pain (28).

Limited evidence indicates no alterations in IL-10 levels for total pain scores or pain interference (LoC 3). Moderate evidence indicates no alterations in IL-10 levels for pain intensity (LoC 2). Limited evidence indicates no alterations in IL-10 levels in cancer survivors experiencing chronic pain compared to the same cancer population without experiencing pain (LoC 3).

IL-4 and IL-13

Relationship With Chronic Pain and Comparison Between Pain and Pain-Free Cancer Survivors

IL-4 and IL-13 levels were explored by 2 studies investigating breast and prostate cancer survivors (28,31). A weak negative correlation between combined BPI scores independent of time points and IL-4 levels was reported for total pain scores but not for pain intensity one month post-chemotherapy. No significant relationships were reported for IL-13 and total pain (n = 1) or pain intensity (n = 1). Further, no alterations in both cytokine levels were found when comparing cancer survivors with and without chronic pain (28).

Limited evidence indicates a weak negative correlation between IL-4 and total pain scores but no alterations in pain intensity (LoC 3). Limited evidence indicates no alterations in IL-13 levels for total pain scores or pain intensity (LoC 3). Limited evidence indicates no alterations in IL-4 or IL-13 levels in cancer survivors experiencing chronic pain compared to the same cancer population without experiencing pain (LoC 3).

IL-1β, IL-5, IL-12, IL-17, IFN-γ and GM-CSF

Relationship With Chronic Pain and Comparison Between Pain and Pain-Free Cancer Survivors

The following 6 cytokines were studied by both Al-Mazidi et al (28) and Fazzari et al (31): IL-1β , IL-5, IL-12, IL-17, IFN-γ and GM-CSF. A weak negative correlation between combined BPI scores and cytokine levels was reported for these 6 cytokines. Further, there were no significant changes between pain intensity and these cytokine levels. In addition, no alterations were found when comparing cancer survivors with and without chronic pain (28). To note, Honerlaw et al (32) attempted to identify IL-1β, IL-12, and IFN-γ levels; however, cytokine levels were undetectable, and therefore no conclusion was made.

Limited evidence indicates a weak negative correlation between IL-1β , IL-5, IL-12, IL-17, IFN-γ and GM-CSF levels and total pain scores but no alterations for pain intensity (LoC 3).

Limited evidence indicates no alteration in cytokine levels in cancer survivors experiencing chronic pain compared to the same cancer population without experiencing pain (LoC 2).

Other Cytokines

Relationship With Chronic Pain

The remaining 18 cytokines (i.e., IL-1α, IL-1, IL-2, IL-7, IL-9, IL-15, IL-23, CCL3, CCL4, CCL5, Eotaxin, FGF, G-CSF, MCP-1, PDFG-bb, TGF-β, IP-10, and VEGF) were investigated by only one study (28,31,34). Of those, both IL-2 and IL-23 showed a weak negative correlation with total pain scores (31). None of the other 16 cytokines showed altered levels for total pain scores, pain intensity, or pain interference (28,34).

Limited evidence indicates a relationship between IL-2 or IL-23 levels and total pain scores. Furthermore, limited evidence indicates no alterations in the levels of the abovementioned 16 cytokines for total pain scores, pain intensity, or pain interference (LoC 3).

Comparison Between Pain and Pain-Free Cancer Survivors

Only one study investigated alterations in cancer

survivors with chronic pain compared to those without (28). The cytokine levels of IL-15, CCL4, CCL5, IP-10, and VEGF were significantly increased in survivors experiencing chronic pain compared to survivors without pain. In addition, no alteration was found for the following 10 cytokines: IL-1α, IL-1, IL-7, IL-9, CCL3, Eotaxin, FGF, G-CSF, MCP-1, and PDFG-bb.

Limited evidence indicates elevated IL-15, CCL4, CCL5, IP-10, and VEGF levels in cancer survivors with pain compared to survivors without pain. Besides, little evidence indicates no alterations in the following cytokine levels: IL-1α, IL-1, IL-7, IL-9, CCL3, Eotaxin, FGF, G-CSF, MCP-1, PDFG-bb (LoC 3).

Discussion

To the best of our knowledge, this is the first systematic review summarizing evidence concerning: 1) the relationship between cytokine levels in cancer survivors experiencing chronic pain, and 2) potential differences in altered cytokine levels between cancer survivors with and without chronic pain. We hypothesized that cytokines levels are disturbed in cancer survivors with chronic pain. In this review, 30 cytokines were featured of which 12 were investigated in 2 or more articles. IL-6, the most discussed pro-inflammatory cytokine, showed moderate evidence for correlations with pain intensity, and an increase was found in cancer survivors with chronic pain compared to pain-free survivors. However, conflicting results were found for both total pain scores and pain interference. First, the study of Fazzari et al (31) was the only study that did not find a significant relationship between total pain scores and IL-6 using a simple univariate regression analysis independent of time points. Interestingly, this study reported that participants entered the study with low to moderate pain, and an upward trend was noticed over time. This is in contrast to the study of Starkweather et al (35), where participants were classified with grade 2 or 3 neuropathy, and the study of Boland et al (29), where 67% of the participants showed signs of sensory neuropathy at the time of assessment. So, a possible explanation of these surprising results is the presence or absence of neuropathy and/or the amount of pain experienced.

Secondly, the study of Fazzari et al (31) reported withdrawing the blood samples in the morning while participants were sober, whereas the other studies did not mention time points. However, diurnal variation of IL-6 levels is already investigated and is known to show a breakthrough in the morning and thus could have led to different conclusions (37).

Thirdly, 2 studies investigated the relationship of IL-6 with pain interference in 2 different cancer populations (i.e., multiple myeloma and endometrial cancer), showing conflicting results (29,32). It is therefore important to mention that due to tumor heterogeneity, each cancer subtype, as well as the presence of metastases, alters the immune system in specific ways (31,38-40). Consequently, results alter depending on the cancer type, for example; despite the lack of association with any pain outcome, limited evidence was found for increased IL-8 levels in survivors of prostate cancer with chronic pain compared to pain-free survivors. Surprisingly, in contradiction to our hypothesis, the pro-inflammatory cytokines except IL-6 showed limited to moderate evidence for no association with any pain outcome. Although the paper of Yehia et al (33) reported a significant association between TNF-α and neuropathy grade 2, this group consisted of only one cancer survivor. Consequently, the sample size was statistically too small, and therefore this result was excluded to state the LoC.

In literature, several pro-inflammatory cytokines are discussed in pathological pain conditions. Similarly, enhanced synthesis of IL-6 and dysregulation of its receptor is associated with pathological pain due to its contribution to pain by central sensitization (41). Interestingly, the systematic review by Canli et al (42) investigating cytokine alterations in chronic low back pain (CLBP) and chronic whiplash-associated disorder (CWAD) found similar results as in this review: (i) moderate evidence was found for no association between CLBP and IL-2, IFN-γ, TNF-α, and (ii) limited evidence was found for no association between TNF-α and CWAD. However, conflicting evidence was found for CLBP and IL-6 (42). To note, the authors did not make a distinction on pain outcomes based on the used questionnaires. In fact, a significant correlation was obtained between the MPQ-SF (total pain scores) and IL-6, whereas conflicting correlations were found for pain intensity questionnaires (42). This indicates that the choice of pain outcome, more specifically the aim of the pain questionnaire or the measured construct, can influence the obtained findings. Moreover, some genes related to pain are already associated with chronic pain disorders or cancer-related pain, including the genes of TNF-α, IL-5, IL-6, IL-10, and IL-17 (41,43,44).

Furthermore, anti-inflammatory cytokines were also discussed in this review. Limited evidence demonstrated no alterations in anti-inflammatory cytokine levels (i.e., IL-10, IL-11, IL-13) when comparing

cancer survivors with pain with those without pain. Furthermore, limited to moderate evidence showed no alterations in any pain measurements for both IL-10 and IL-13, although a negative correlation for IL-4 with average pain was found (LoC 3). However, lower cytokine levels of IL-10 were identified in chronic pain disorders compared to healthy controls (42,45). Interestingly, polymorphisms of the genes IL-4 and IL-10 showed already an association with other chronic pain states (46,47).

Results should be interpreted with caution as several limitations have been noticed. First, to be included in this review, studies had to assess both cytokine levels and chronic pain outcomes following cancer treatment at the same time point. Because chronic pain following cancer is still underrecognized, only a small amount of post-cancer treatment studies specifically assessed chronic pain outcomes in combination with cytokine levels. Subsequently, RCTs could be included if the research questions could be answered, but since only data within the groups were used, they were regarded as cross-sectional studies for grading the evidence. This led to a moderate LoC at most, as all studies received a level of evidence B (case-control and cohort study) or C (cross-sectional study). Moreover, all studies showed a moderate RoB except one, which received a high RoB. Most studies lost points because the pain experience was measured using self-reported questionnaires or the choice of hospital controls over community controls. However, the golden standard is the use of self-reported validated questionnaires for the assessment of a person's pain experience (22). In addition, cancer itself influences the immune system. This makes the choice of pain-free cancer survivors as control group more interesting than community controls. However, including healthy controls as well would be of added value. In conclusion, these 2 criteria, i.e., self-reported pain questionnaires and the choice of hospital controls over community controls, are hard to overcome when investigating inflammatory markers such as cytokines in relation to pain within cancer survivors. Secondly, the included articles contained a wide variety of cancer types, treatments, and methodologies. Nevertheless, the results were most of the time straightforward. Lastly, the term chronic pain was defined as 3 months post-diagnosis in this review. However, ideally, it was considered 3 months post-treatment so there would be no overlap with acute pain due to the sequence of different cancer treatments over time. Despite some limitations, the strength of this review is the elaboration on both relationships and comparisons. Further, it distinguished different pain outcomes based on the constructs measured.

To summarize, this review features 8 articles that studied 30 cytokines for their relationship to chronic pain. Although 6 different cancers, a variety of treatments, and methodologies were included, the results were most of the time straightforward. IL-6 was the most discussed cytokine and showed moderate evidence for a correlation with pain intensity and is elevated in cancer survivors experiencing chronic pain compared to pain-free survivors. For the second most discussed cytokine, TNF-α, moderate evidence showed no correlation with any pain experience. Also, moderate evidence for no association with pain intensity was found for IL-8 and IL-10. All other featured cytokines and pain outcomes provided limited evidence. This illustrates the need for more post-cancer treatment studies in all cancer populations whereby the same validated methodology is used to identify both pro- and anti-inflammatory cytokine levels as well as constructs to measure chronic pain among different cancer (sub) populations.

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Appendix 1. ***Adapted search strategies for specific databases***.

PubMed 6/12/2021
((neoplasms [MeSH Terms]) OR (carcinoma[MeSH Terms]) OR (cancer) OR (neoplasm) OR (carcinoma)) AND ((chronic pain[MeSH Terms]) OR (pain, postoperative[MeSH Terms]) OR (pain, intractable[MeSH Terms]) OR (neuralgia[MeSH Terms]) OR (central nervous system sensitization[MeSH Terms]) OR (1) OR (persistent pain) OR (neuropathy) OR (neuropathic pain) OR (nociplastic pain) OR (central sensitization) OR (nociceptive pain)) AND ((inflammation) OR (cytokine) OR (neuroinflammation) OR (interleukin) OR (tumor necrosis factor) OR (IL) OR (TNF) OR (neurogenic inflammation[MeSH Terms]) OR (cytokines[MeSH Terms]) OR (inflammation[MeSH Terms]) OR (nervous system inflammation)) Filters: Humans, Dutch, English, French, German, Adult: 19+ years, Aged: 65+ years, from 2000 – 2021
Web Of Science 17/12/2021
TS=((neoplasms) OR (cancer)OR (neoplasm) OR (carcinoma)) AND ((chronic pain) OR (post-operative pain) OR (postoperative pain) OR (intractable pain) OR (neuralgia) OR (persistent pain) OR (neuropathy) OR (neuropathic pain)OR (nociplastic pain) OR (central nervous system sensitization) OR (central sensitization) OR (nociceptive pain) AND ((cytokine) OR (neuroinflammation) OR (interleukin) OR (tumor necrosis factor) OR (IL) OR (TNF) OR (neurogenic inflammation) OR (cytokines) OR (nervous system inflammation) OR (inflammation)) Filters: Publication years (2000-2022), English, German, French, Document types (Articles or Meeting Abstracts)
Embase 2/12/2021
('neoplasm'/exp OR 'carcinoma'/exp OR cancer OR neoplasms) AND ('chronic pain'/exp OR 'chronic intractable pain' OR 'chronic pain' OR 'pain, chronic' OR 'persistent pain') AND ('postoperative pain'/exp OR 'pain, postoperative' OR 'post operation pain' OR 'postoperative pain' OR 'neuralgia'/exp OR 'central nervous system sensitization'/exp OR 'central nervous system sensitisation' OR 'central nervous system sensitization' OR 'central sensitization'/exp OR 'neuropathic pain'/exp OR 'neuropathic pain' OR 'pain, neuropathic' OR 'neuropathy'/exp OR 'nociplastic pain'/exp OR 'nociceptive pain'/exp OR 'nociceptive pain' OR 'pain'/exp) AND ('cytokine'/exp OR 'cytokine' OR 'cytokines' OR 'interleukin' OR 'tumor necrosis factor'/exp OR 'tnf alfa' OR 'tnf alpha' OR 'cachectin' OR 'cachetin' OR 'human recombinant tumour necrosis factor alpha' OR 'mhr 24' OR 'recombinant tumour necrosis factor alpha' OR 'tissue necrosis factor' OR 'tumor necrosis factor' OR 'tumor necrosis factor alfa' OR 'tumor necrosis factor alpha' OR 'tumor necrosis factor-alpha' OR 'tumor necrosis factors' OR 'tumor necrosis serum' OR 'tumour necrosis factor' OR 'tumour necrosis factor alfa' OR 'tumour necrosis factor alpha' OR 'tumour necrosis factor-alpha' OR 'tumour necrosis factors' OR 'tumour necrosis serum' OR 'nervous system inflammation'/exp OR 'inflammation, nervous system' OR 'nervous system inflammation' OR 'neuroinflammation' OR 'neurogenic inflammation'/exp OR 'inflammation, neurogenic' OR 'neurogenic inflammation' OR 'inflammation'/exp) Filters: Publication years (2000-2022), languages, humans, adult, aged, article, article in press, conference paper, preprint