Brain, Behavior, & Immunity - Health 46 (2025) 100995

Contents lists available at ScienceDirect

Brain, Behavior, & Immunity - Health

journal homepage: www.editorialmanager.com/bbih/default.aspx

Mental distress and inflammation in bladder cancer: The nerve makes things less vague

Iveta Mikolaskova [a], Yori Gidron [b], Vladimira Durmanova [a], Magda Suchankova [a], Maria Bucova [a], Luba Hunakova [a,*]

[a] Institute of Immunology, Faculty of Medicine, Comenius University in Bratislava, Odborarske namestie 14, 811 08, Bratislava, Slovakia
[b] Department of Nursing, Faculty of Welfare and Health Sciences, University of Haifa, Haifa, 3498838, Israel

ARTICLE INFO

Keywords:
Bladder cancer
Heart-rate variability
Inflammation
Distress
Life-satisfaction
Moderation

ABSTRACT

Objectives: This study aimed to explore the interaction between perceived stress, life satisfaction, heart rate variability (HRV), and immune-inflammatory markers in bladder cancer patients. We investigated how HRV moderates the relationship between psychological distress and levels of TNF-α and TGF-β cytokines. We hypothesized that high vagal nerve activity, as indicated by higher HRV, mitigates the impact of perceived stress and life dissatisfaction on inflammation.

Methods: The study included 73 patients with bladder cancer. HRV was determined from a 5-min ECG recording, focusing on the standard deviation of normal-to-normal interbeat intervals (SDNN). Psychological distress was measured using the Perceived Stress Scale (PSS), and life satisfaction was evaluated with the Life Satisfaction Questionnaire (LSQ). Serum concentrations of TNF-α and plasma levels of TGF-β were determined using sandwich ELISA.

Results: We found evidence that HRV modulates the relation between perceived stress and inflammation. In patients with low HRV (SDNN $<$20 ms), PSS was positively correlated with serum level of TNF-α and negatively with the level of TGF-β, while life satisfaction was positively correlated with TGF-β. These relationships were not significant in patients with high HRV (SDNN $\geq$20 ms).

Conclusion: Our findings suggest that high vagal activity, as indicated by higher HRV, may mitigate the adverse effects of psychological distress on immune-inflammatory responses in patients with bladder cancer. Stress-related inflammation took place under conditions of low HRV, highlighting the potential role of autonomic regulation in cancer prognosis. Future research should further explore these relationships to develop interventions aimed at improving patient outcomes through stress management and enhanced vagal nerve activity to regulate inflammation in cancer.

1. Introduction

Stress is an inevitable part of life and one of the fundamental survival mechanisms. However, chronic stress is accompanied by a broad spectrum of negative impacts on the brain, neuroendocrine system, immunity, inflammation, and various organ systems (Arnsten et al., 2015). Activation of the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS) by chronic stress leads to the decline and dysfunction of the prefrontal cortex and hippocampus (Arnsten et al., 2015). After activation, the SNS releases catecholamines, including epinephrine and norepinephrine, via sympathetic nerve fibers and the adrenal medulla, while the HPA axis increases the release of glucocorticoids from the adrenal cortex. These stress hormones can promote tumorigenesis and cancer development through various mechanisms (Wang et al., 2022). Catecholamines and glucocorticoids accelerate tumorigenesis by promoting DNA damage, gene mutations, and preventing tumour cells from undergoing autophagy and apoptosis (Wang et al., 2022; Flint and Bovbjerg, 2012; Roy et al., 2018; Zhang et al., 2019).

The prolonged release of glucocorticoids, with their inhibitory effects on multiple types of immune cells during chronic stress, can attenuate the activity of anti-tumour Th1 immunity, the activation of regulatory T cells, and the production of myeloid-derived suppressor cells, which can lead to the long-lasting release of proinflammatory

* Corresponding author.
E-mail address: luba.hunakova@fmed.uniba.sk (L. Hunakova).

https://doi.org/10.1016/j.bbih.2025.100995
Received 23 October 2024; Received in revised form 14 March 2025; Accepted 12 April 2025
Available online 14 April 2025

cytokines, resulting in the development of chronic low-grade inflammation (Cain and Cidlowski, 2017; Kluckova et al., 2020). Both decreased adaptive cell-mediated immunity and increased inflammation have pro-tumorigenic effects (Cain and Cidlowski, 2017; Dai et al., 2020; Hanahan, 2022; Kluckova et al., 2020).

The inflammatory process plays a role in all phases of tumorigenesis - initiation, promotion, and progression - and immune cells and mediators can contribute to tumour growth during chronic inflammation (Balkwill and Mantovani, 2001; Yao et al., 2019). Proinflammatory cytokines, such as TNF, IL-1, and IL-6, can also activate the release of glucocorticoids, forming a second loop of HPA axis activation through cytokines (Dunn, 2000).

Moreover, in cancer patients, various psychological stressors, such as being informed of a cancer diagnosis, undergoing surgery, the presence of malignant tissue, and related inflammation, can trigger stress responses. These processes, along with anxiety, depression, and rumination about cancer, are perceived and processed by the central nervous system (CNS), which could further potentiate the stress response, inflammation, and decreased adaptive immunity, thus potentiating carcinogenesis (Eckerling et al., 2021; Menard et al., 2017; Cai et al., 2024).

Concerning inflammation, most research considers tumour necrosis factor alpha (TNF-α) as primarily a pro-inflammatory cytokine (Haapakoski et al., 2015; Tylutka et al., 2024), and transforming growth factor beta (TGF-β) as a cytokine with potent immunosuppressive (and indirectly anti-inflammatory) activities (Yoshimura et al., 2010). TGF-β downregulates Th1 cell-mediated immunity, depressing the activity of T helper and cytotoxic lymphocytes, natural killer (NK) cells, and macrophages. Macrophages with attenuated Th1-driven activation exhibit reduced antimicrobial and anti-tumour activity, along with a decreased capacity to produce proinflammatory cytokines (Yoshimura et al., 2010; Stolfi et al., 2020). Moreover, TGF-β increases the differentiation of anti-inflammatory M2 macrophages, which have immunosuppressive activity (Stolfi et al., 2020). Recent studies have revealed roles for TGF-β in tumour immune evasion (Tauriello et al., 2022). TGF-β released by cancer cells, stromal fibroblasts, and other cells in the tumour microenvironment creates an immunosuppressive environment that further promotes cancer progression and metastasis while preventing or attenuating the efficacy of anticancer immunotherapies (David and Massagué, 2018; Derynck et al., 2021; Pickup et al., 2017).

In our study, TNF-α was chosen as a pro-inflammatory cytokine and TGF-β as an immunosuppressive and anti-inflammatory cytokine, both of which play roles in tumour progression and immune regulation. TNF-α, initially identified for its properties of inducing tumour necrosis, is also recognized as a driver of chronic inflammation and tumorigenesis via NF-κB activation, reinforcing a positive feedback loop that sustains inflammation and cancer progression. TNF-α has been implicated in multiple malignancies, including breast, colorectal, pancreatic, and liver cancers, where it promotes epithelial-mesenchymal transition (EMT), angiogenesis, and metastasis. In bladder cancer, TNF-α enhances tumour migration and invasion via the p38 MAPK signalling pathway (Mercogliano et al., 2021), which is known for transducing stress signals from the environment (Martínez-Limón et al., 2020). Dysregulation of TGF-β signalling plays a role in tumour progression, exhibiting tumour-suppressor properties in early stages but often shifting toward immune suppression and tumour-promoting functions. In bladder cancer, genetic variations in TGF-β pathway components, such as SMAD proteins, have been linked to increased cancer risk and progression (Stojnev et al., 2019). Additionally, transgelin, an actin-binding protein involved in EMT, promotes bladder cancer metastasis and is upregulated by TGF-β, which enhances cancer cell migration (Li and Wu, 2019; Chen et al., 2019).

In our study we focused on bladder cancer patients. This type of cancer is a prevalent malignancy with significant morbidity and mortality, accounting for approximately 614,000 new cases and more than 200,000 deaths worldwide in 2022 (Bray et al., 2024). The disease burden is particularly higher among men than women, and with increasing mortality rates being reported among men in Thailand, Israel, and Slovakia according to Global cancer statistics 2022 (GLOBOCAN) (Bray et al., 2024). The mortality rate is projected to increase by up to 54 % for men and to more than double or nearly triple for women globally by 2040 (Wéber et al., 2024).

The psychological distress can be one of the factors that could play a role in the disease development as well as can exacerbate the overall health condition following the initial diagnosis and treatment of the disease (Eckerling et al., 2021; Liu et al., 2022). Both experimental and clinical studies suggest that the effects of stress on tumorigenesis and the course of cancer can be achieved by an imbalanced autonomic nervous system (Makale et al., 2017). Mental and physical distress have been reported in pancreatic, breast and ovarian cancer patients before the cancer diagnosis (Li et al., 2023; Van Esch et al., 2012; Vine et al., 2003). Another meta-analysis from 16 prospective cohort studies in initially cancer-free individuals has demonstrated an association between psychological distress and different types of cancer onset and death, but predominantly with colorectal and prostate cancer (Batty et al., 2017). Similarly, psychological distress has been associated with worse prognosis in breast cancer patients (Brown et al., 2020) and increased cancer mortality in individuals with cancer history, particularly in lung cancer (Hamer et al., 2009).

Psychological distress, including perceived stress, negative emotional responses, poor quality of life or life dissatisfaction, has been linked to adverse health effects and increased inflammation, potentially influencing cancer outcomes (Chida et al., 2008). Long-lasting psychological distress has been shown to exacerbate chronic inflammation and enhance immunopathologic mechanisms (Antoni and Dhabhar, 2019). One of the regulators of stress responses involves the vagus nerve. Its activity is indexed by heart rate variability (HRV), a measure of autonomic nervous system (ANS) function, reflecting the degree of change in the intervals between normal heart-beats. HRV reflects the balance between the sympathetic and parasympathetic branches. HRV mirrors the heart's capacity to respond to distress (Kim et al., 2018). Previous research has emphasised vagally-mediated HRV's predictive role in cancer (De Couck et al., 2018), and has suggested that high vagal nerve activity may mitigate the effects of stress on inflammation (Tracey, 2002), reduce the excessive sympathetic responses, and enhance protective effects across diverse conditions (De Couck et al., 2012). The vagus nerve plays an important role in regulating immune responses through the "inflammatory reflex," a mechanism by which the CNS modulate inflammation via ANS, particularly involving the splenic sympathetic anti-inflammatory pathway, the HPA axis and the cholinergic anti-inflammatory pathway. The latter is mediated by acetylcholine, which binds to α7 nicotinic acetylcholine receptors (α7nAChR) on macrophages and other immune cells, leading to a protective reduction in the release of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β, while preserving the release of anti-inflammatory cytokines such as IL-10 and TGF-β (Pavlov and Tracey, 2012; Johnston and Webster, 2009; Bonaz et al., 2016). Moreover, activation of the HPA axis, through the release of cortisol and other hormones also acts anti-inflammatory. Thus, vagus nerve regulation facilitates endogenous neuroimmune pathways, contributing to inflammation control and improved

autonomic balance (Liu et al., 2024).

Furthermore, high HRV predicts longer cancer survival (De Couck et al., 2018; Zhou et al., 2016) and moderates the effects of other prognostic factors, such as relapse, in cancer (Atar et al., 2023). These all highlight the potential moderating role of HRV in the relationship between psychological distress and immune-inflammatory responses and cancer prognosis.

This study aims to explore the interaction between perceived stress, life satisfaction, HRV, and inflammatory markers in bladder cancer patients. Specifically, we investigated the correlations between perceived stress and life satisfaction and HRV with proinflammatory TNF-α and immunosuppressive and anti-inflammatory TGF-β. In addition, we tested whether HRV (indexed by SDNN - the standard deviation of normal-to-normal interbeat intervals) moderates the relationship between psychological distress and levels of TNF-α and TGF-β. We hypothesized that high vagal nerve activity, as indicated by higher HRV, will mitigate the impact of perceived stress and life dissatisfaction on inflammation. Understanding this moderation would be a testimony for the protective roles of the vagal nerve and is essential for developing targeted interventions to improve patient outcomes.

2. Methods

2.1. Study population and enrolment

The study cohort comprised 73 individuals over the age of 18 from the Urology Clinic of St. Cyril and Methodius Hospital in Bratislava. Participants included both patients with a primary diagnosis of bladder cancer and those experiencing a recurrence, all of whom were undergoing transurethral resection of bladder tumours (TURBT). Exclusion criteria encompassed those with diabetes mellitus, coronary artery disease, left ventricular hypertrophy, valvular heart disease, cardiac pacemaker, or any other malignancies diagnosed within the past five years. Additionally, individuals on cardiac glycosides, anti-arrhythmic drugs, any type of anti-depressive and anti-psychotic drugs, or atropines were excluded, as were those with poor ECG quality or more than 10 % ectopic beats. Blood samples and ECG recordings for HRV analysis were collected from patients in a seated position, either one day prior to or on the day of surgery. The study was conducted from November 2021 to June 2024, adhering to the International Ethical Guidelines and the Declaration of Helsinki. Written informed consent was obtained from all participants, and the study received approval from the Ethics Committees of both the Hospital of St. Cyril and Methodius (EK 1/2/2022) and the Faculty of Medicine, Comenius University in Bratislava (125/2021).

2.2. Biological sample analysis

Serum concentrations of tumour necrosis factor alpha (TNF-α), along with plasma concentrations of transforming growth factor beta (TGF-β), were determined using sandwich ELISA tests. The assays were conducted following the protocols specified by the human ELISA kits: TNF-α from FineTest, China, and TGF-β from R&D Systems, USA.

2.3. HRV assessment

HRV measurements were obtained using a 5-min ECG recording. Before the recording, patients rested in a supine position for 10 min, then sat upright for the ECG recording, using the Bittium Faros 180 device (Bittium Biosignals Ltd, Finland). Electrodes were placed on the right first and left fifth intercostal spaces at the midclavicular line after skin preparation with ethanol. A 1000 Hz sampling rate was employed to capture the electrical signal. HRV analysis was performed using the Kubios Premium software (Kubios Oy, Finland), which extracted R-R intervals, measured in milliseconds, from the R peaks of the QRS complexes in the ECG signal. This analysis provided HRV parameters to assess the autonomic nervous system (ANS) balance and activity, focusing on parameters linked to the sympathetic and parasympathetic branches. The primary HRV parameter analyzed for parasympathetic activity was the time-domain measure of the standard deviation of normal-to-normal inter-beat intervals (SDNN, ms.).

2.4. Psychological assessment

Psychological assessment utilized the Perceived Stress Scale 10 (PSS-10) (Cohen et al., 1994), which measures the extent to which participants perceive their lives as unpredictable, uncontrollable, overwhelming and stressful, through 10 items, some of which are reverse-scored. PSS scores range from 0 (no perceived stress) to 40 (high perceived stress).

The Life Satisfaction Questionnaire (LSQ) (Fahrenberg et al., 2001) was used to evaluate participants' satisfaction across various domains, including physical and mental health, work and employment, financial situation, leisure time, marriage and partnership, relationships with children, self-perception, sexuality, friends and relatives, and housing. Satisfaction was rated on a 7-point Likert scale from 1 (very dissatisfied) to 7 (very satisfied). Domain scores were calculated by summing the scores of the 7 items within each domain, yielding a possible range of 7–49. Scores for work and employment, marriage and partnership, and relationships with children were not included to the total score due to frequently missing data. The scores were then converted to standardized scores according to the LSQ scoring manual based on age and sex, with higher scores indicating greater life satisfaction.

2.5. Statistical analysis

We first performed descriptive statistics (means, standard deviations, and percentages). Then, we examined the correlations between the psychological variables and cytokines using Pearson correlations in the full sample. To examine the moderating effects of HRV, we conducted a hierarchical multiple regression, testing the additional contribution of the interaction terms PSS × SDNN and LSQ × SDNN in relation to TNF-α and TGF-β, after statistically controlling for age, tumour grade, and the main effects of SDNN and either PSS or LSQ. These tests were followed by Pearson correlations between PSS and LSQ with TNF-α and TGF-β, separately in patients with low SDNN and high SDNN, split at 20 ms, in line with our previous studies (De Couck et al., 2016).

Table 1
Descriptive statistics in bladder cancer patients.

	Bladder cancer patients
	n = 73
Age (years – mean, SD)	67.00 (8.99)
Males (n)	50
Females (n)	23
BMI (mean, SD)	27.65 (4.65)
NMIBC (n)	55
Low grade (n)	31
High grade (n)	24
MIBC (n)	18
High grade (n)	18
TNF-α (pg/ml) (mean, SD)	164.29 (451.84)
TGF-β (pg/ml) (mean, SD)	130.97 (11.33)
PSS (score) (mean, SD)	15.75 (5.35)
LSQ (score) (mean, SD)	6.68 (2.02)
SDNN (ms) (mean, SD)	17.58 (9.87)

Note: BMI = body mass index; SD = standard deviation; NMIBC = non-muscle invasive bladder cancer (pTa, carcinoma in situ/CIS, and pT1 stages); MIBC = muscle-invasive bladder cancer (pT2 and pT3 stages); TNF-α = Tumour necrosis factor alpha; TGF-β = Transforming growth factor beta; PSS = Perceived stress scale; LSQ = Life satisfaction questioner score; SDNN = Standard deviation of normal-to-normal interbeat intervals.

3. Results

3.1. Basic characteristics of bladder cancer patients

The study sample consisted of 73 individuals, with 50 males and 23 females. The mean age (±SD) was 67.00 years (8.99), and the mean BMI (±SD) was 27.65 (4.65). All participants were diagnosed with bladder cancer. Table 1 provides a summary of the descriptive characteristics of patients.

3.2. Association of perceived stress and life satisfaction with immune-inflammatory parameters, as function of HRV

The correlations of PSS and LSQ scores with the immune-inflammatory parameters in the full sample are shown in Table 2. PSS tended to be positively correlated with TNF-α and tended to be negatively correlated with TGF-β. LSQ only tended to be positively correlated with TGF-β.

We then investigated the interaction effects of PSS and LSQ scores with HRV (SDNN), in relation to both immune-inflammatory markers. The interaction between PSS and SDNN in relation to log-transformed TGF-β levels tended to be significant (F-change (1,67) = 2.83, $p < 0.10$). Additionally, the interaction of PSS and SDNN significantly predicted log-transformed TNF-α levels (F-change (1,65) = 7.27, $p = 0.009$). We stratified patients into two groups based on their HRV (low SDNN <20ms vs. high SDNN ≥20ms) to examine the relationship between psychological distress and immune-inflammatory markers. In patients with low HRV (SDNN <20ms), PSS was positively correlated with TNF-α ($r = 0.316$, $p = 0.029$) and negatively correlated with TGF-β ($r = -0.308$, $p = 0.029$), independent of age and cancer grade. Additionally, the LSQ score was positively correlated with TGF-β ($r = 0.281$, $p = 0.048$). Conversely, in patients with high HRV (SDNN ≥20ms), PSS and LSQ were not significantly related to either TNF-α or TGF-β. These results are shown in Table 3. Fig. 1 illustrates the selected association of TNF-α with PSS in patients with low vs. high SDNN. We used the cut-off of 20 ms for SDNN since this cut-off was found in several past studies to predict survival in patients with different cancers (De Couck et al., 2016) and is the median of SDNN in several cancers together (De Couck et al., 2013).

4. Discussion

In this study, we found that TGF-β was negatively associated with perceived stress (PSS) and positively associated with life satisfaction (LSQ), whereas TNF-α was positively associated with PSS—both only in patients with low HRV. These findings suggest that high vagal nerve activity may play a role in modulating the relationships between perceived stress and cytokine levels in bladder cancer patients. Specifically, the associations between perceived stress and two immune-inflammatory cytokines observed in low-HRV patients were not present in those with high HRV, which could indicate a potential buffering effect of high HRV for these associations.

Table 2
Pearson correlations between perceived stress and life satisfaction with immune-inflammatory parameters.

		log TNF-α	log TGF-β
PSS	Pearson correlation, r	0.198	−0.208
	Sig. (2-tailed)	0.097	0.078
LSQ	Pearson correlation, r	−0.045	0.221
	Sig. (2-tailed)	0.708	0.060

Note: PSS = Perceived stress scale; LSQ = Life satisfaction questioner score; TNF-α = Tumour necrosis factor alpha; TGF-β = Transforming growth factor beta; r = Pearson correlation coefficient; Sig. (2-tailed) = level of statistical significance, (2-tailed).

Table 3
Pearson correlations between perceived stress and life satisfaction, with immune-inflammatory parameters, in patients with low vs. high vagal nerve activity (SDNN).

			log TNF-α	log TGF-β
Low SDNN <20ms	**PSS**	Pearson correlation, r	0.316	−0.308
		Sig. (2-tailed)	**0.029***	**0.029***
		N	48	50
	LSQ	Pearson correlation, r	−0.065	0.281
		Sig. (2-tailed)	0.663	**0.048***
		N	48	50
High SDNN ≥20ms	**PSS**	Pearson correlation, r	−0.144	0.198
		Sig. (2-tailed)	0.513	0.364
		N	23	23
	LSQ	Pearson correlation, r	0.008	0.017
		Sig. (2-tailed)	0.972	0.938
		N	23	23

Note: SDNN = Standard deviation of normal-to-normal interbeat intervals; PSS = Perceived stress scale; LSQ = Life satisfaction questioner score; TNF-α = Tumour necrosis factor alpha; TGF-β = Transforming growth factor beta; r = Pearson correlation coefficient; Sig. (2-tailed)* = level of statistical significance (2-tailed); N = number of samples.

Vagal activity, reflected by HRV, influences the body's response to stress (Larkin et al., 2021). In our analysis, we observed a negative correlation between PSS and TGF-β levels in patients with low HRV-SDNN. TGF-β is a pleiotropic cytokine involved in immunosuppressive activity (Yoshimura et al., 2010). Disruption of the TGF-β pathway has been implicated in many human diseases, including solid and hematopoietic tumours (Massagué, 2008; Sanjabi et al., 2017).

We found that perceived stress appears to be associated with a reduction of TGF-β plasma level, especially in individuals with low vagal activity. The observed reduction in TGF-β could lead to increased inflammation, creating an environment that may affect cancer dynamics and exacerbate outcomes (Massagué, 2008). Higher vagal activity (high HRV) might buffer these effects, maintaining TGF-β's anti-inflammatory role even under stress conditions. These results are partly in line with findings in B-cell lymphoma, where relapse predicted mortality only in patients with low HRV, whereas in patients with high HRV, relapse no longer predicted mortality (Atar et al., 2023).

Our results also indicate that TGF-β positively correlated with life satisfaction (LSQ) in patients with low HRV-SDNN. LSQ assesses long-term life satisfaction across various domains. This positive correlation indicates that higher life satisfaction is associated with higher levels of TGF-β, potentially reflecting a better-regulated inflammation. Higher vagal activity might provide resilience against chronic stress and is often positively correlated with well-being (Jandackova and Jackowska, 2015; Weber et al., 2010). In addition, high vagal activity reflects better natural regulation of inflammation (Rosas-Ballina et al., 2011). Together, these could lead to a more balanced inflammatory response and regulated TGF-β expression in people with high HRV, regardless of their life satisfaction. These physiological mechanisms could explain the null correlation between LSQ and TGF-β found in patients with high HRV.

Such findings align with the understanding that TGF-β has immunoregulatory properties (Batlle and Massagué, 2019), which can be enhanced by positive psychological states and high vagal tone. However, in patients with low HRV, insufficient biological regulation of stress and inflammation, may result in a stronger association between better life satisfaction and TGF-β, in other words to better regulation of inflammation. It is possible that there is a synergism between high HRV and high LSQ for regulating inflammation due to the following converging evidence. First, as stated above, the vagus inhibits inflammation (Rosas-Ballina et al., 2011). Second, positive well-being is associated with activation of various frontal brain regions including the anterior cingulate and prefrontal regions (King, 2019). Finally, one unique study found that better brain connectivity between the prefrontal

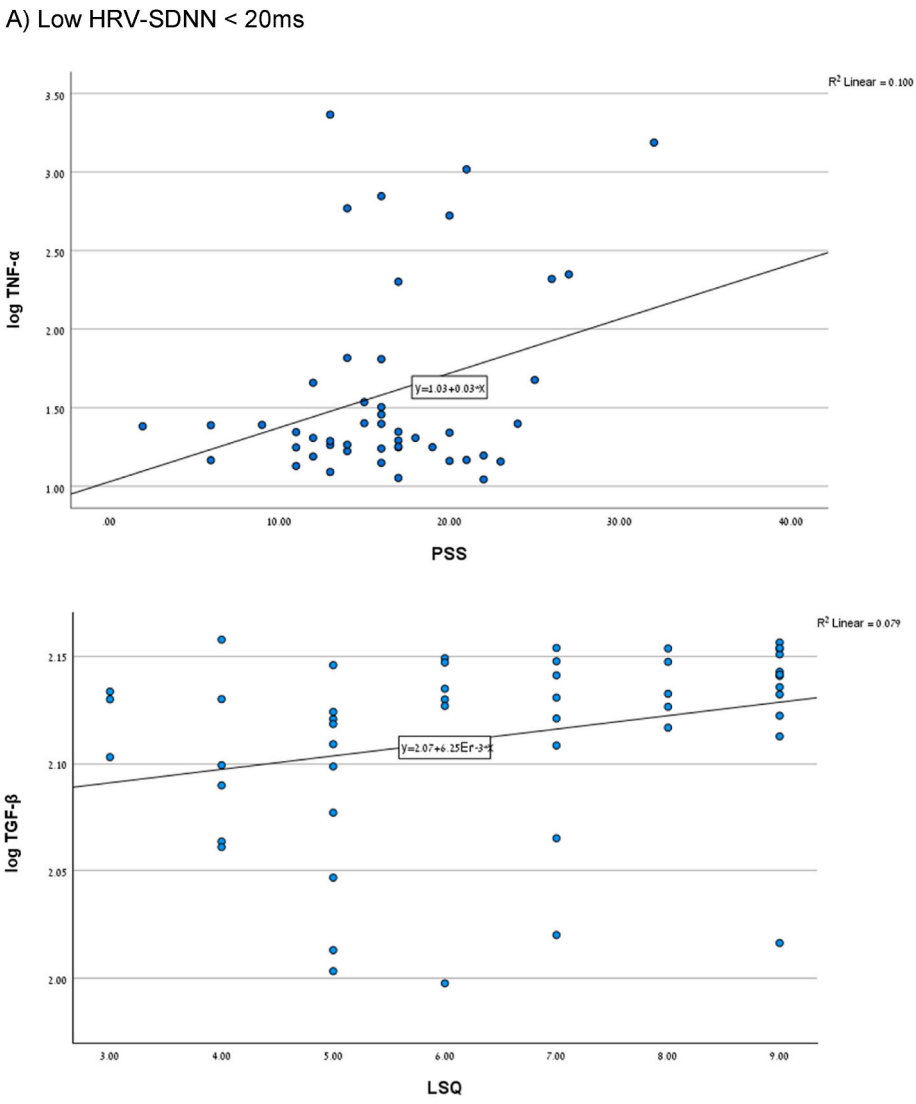

Fig. 1. Association of perceived stress and life satisfaction with TNF-α and TGF-β in relation to low vs. high vagal nerve activity.

cortex and amygdala (a region processing threat) is strongly related to lower inflammation (Mehta et al., 2022).

TGF-β exerts a dual influence on cancer progression, acting as a tumour suppressor in premalignant cells and as a tumour promoter in malignant cells (David and Massagué, 2018). Initially, TGF-β enforces cytostatic and apoptotic responses to prevent uncontrolled proliferation, but genetic alterations can render cancer cells resistant to its suppressive effects. These mutations occur in 25–50 % of gastric, colorectal, and pancreatic adenocarcinomas and 10–20 % of bladder, lung, and head and neck carcinomas (David and Massagué, 2018; Batlle and Massagué, 2019). As tumours evolve, selective pressure enables cancer cells clones to shift TGF-β signalling from growth suppression to immune evasion, stromal remodelling, and EMT induction, fostering invasion and metastasis. Alternatively, cancer cells may reinterpret TGF-β signals to drive tumour-promoting functions (Batlle and Massagué, 2019). Chronic stress and diminished vagal activity may contribute to this oncogenic shift by altering neuroimmune communication and promoting a pro-inflammatory tumour microenvironment.

Impaired vagal signalling has been linked to immune dysregulation, as evidenced by study demonstrating that vagotomy diminishes the immunomodulatory effects of ghrelin and growth hormone, which possess anti-inflammatory and anti-apoptotic properties (Zhou et al., 2020). This disruption led to dysregulated lymphocyte counts and increased inflammation, highlighting the vagus nerve's role in maintaining immune homeostasis. TGF-β, which can induce lymphocyte apoptosis under pathological conditions, is often overproduced by tumours to suppress immune responses, facilitating tumour growth and invasion (Zhou et al., 2020). Chronic stress has been shown to activate TGF-β-SMAD signalling, and blocking this pathway restores pro- and anti-inflammatory cytokine balance (Zhang et al., 2018). Thus, chronic stress and reduced vagal activity may impair the action of anti-inflammatory mediators in maintaining lymphocyte homeostasis, regulating apoptosis-related pathways and pro-inflammatory cytokines (Zhou et al., 2020; Zhang et al., 2018), potentially contributing to an immune environment permissive to oncogenic shift and tumour progression.

The positive association between TNF-α and PSS aligns with existing evidence, suggesting that psychological distress is associated with higher inflammatory responses (Kiecolt-Glaser et al., 2010; Elgellaie et al., 2023). This may then potentially adversely influence cancer progression and patient outcomes (Chida et al., 2008). Elevated levels of pro-inflammatory cytokines such as TNF-α are well-documented in promoting tumour growth, angiogenesis, and immune evasion (Balkwill and Mantovani, 2001; Grivennikov et al., 2010), with poor life

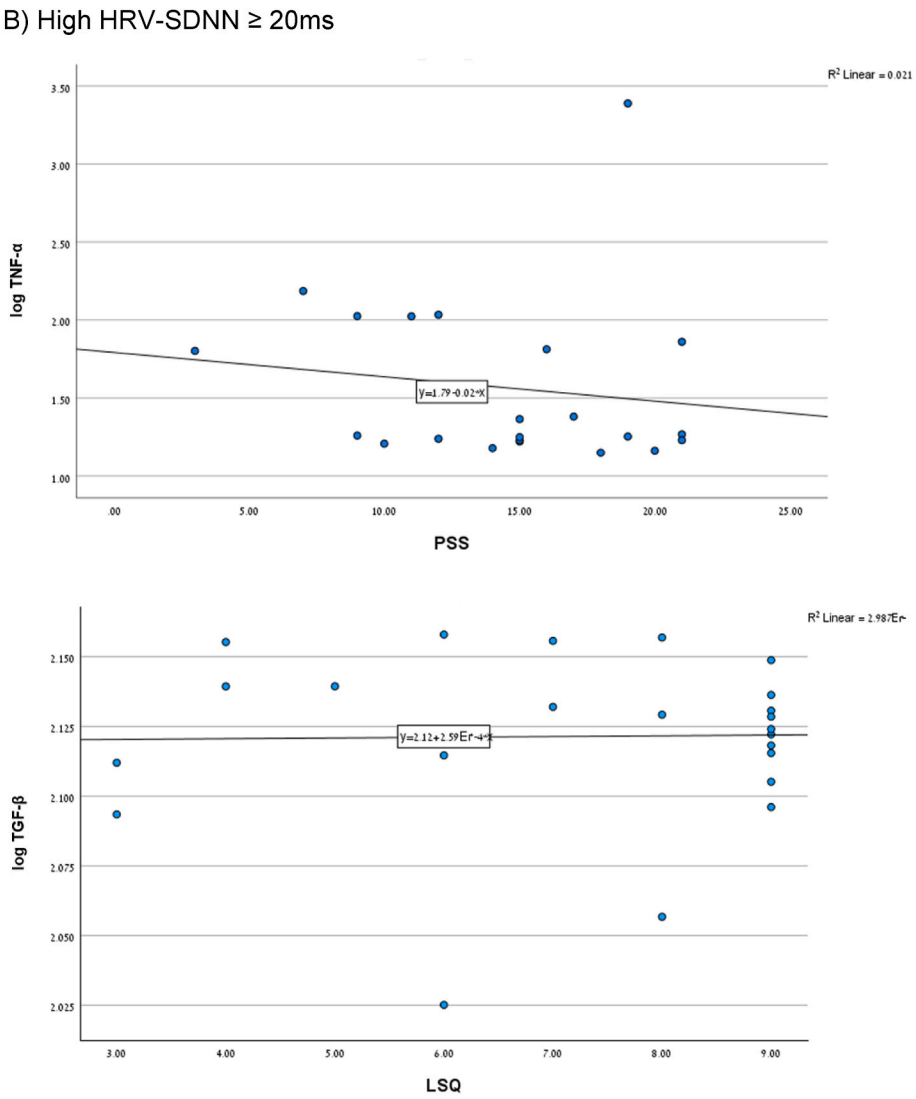

Fig. 1. (*continued*).

satisfaction, stress, and inflammation playing an important role in this relationship (Shrout et al., 2020; McFarland et al., 2022; Ironson et al., 2018; Rosella et al., 2019).

Moreover, the interaction between PSS and SDNN in relation to log-transformed TGF-β levels tended to be significant and the interaction of PSS and SDNN significantly predicted log-transformed TNF-α levels. These findings suggest that the relationship between stress and inflammatory markers is modulated by vagal activity. Specifically, low HRV-SDNN may enhance the impact of perceived stress on inflammatory cytokine levels, indicating that individuals with lower vagally-associated HRV may exhibit higher levels of inflammatory markers (Hunakova et al., 2023; Cooper et al., 2015; Lampert et al., 2008). Similar moderation by HRV has been observed in other studies and systems. In healthy Japanese students, brain activity correlated with peripheral anti-tumour immunity (NK cells) only in those with high HRV, but not in those with low HRV (Ohira et al., 2013). Additionally, in patients with diffuse large B-cell lymphoma, cancer relapse predicted death only in those with low HRV (Atar et al., 2023).

PSS and LSQ were not significantly related to TNF-α or TGF-β levels in patients with high HRV (SDNN ≥20ms). This suggests that high vagal nerve activity may buffer the effects of psychological distress on inflammatory processes, potentially reducing the risk of adverse cancer outcomes. These findings are consistent with previous studies demonstrating the regulatory effects of high HRV, as vagally-related HRV parameters have been negatively correlated with inflammatory markers, and higher vagal activity has also been associated with reduced production of proinflammatory cytokines (Hunakova et al., 2023; Marsland et al., 2007). This underscores the importance of autonomic regulation in cancer biology. High HRV, indicative of greater parasympathetic (vagal) activity, appears to attenuate the inflammatory response to psychological stress. This is also in line with the polyvagal theory, which posits that the vagus nerve plays a critical role in regulating the inflammatory response and maintaining homeostasis (Porges, 2007), as shown in pancreatic cancer patients (De Couck et al., 2016) and other studies emphasizing vagally-mediated HRV's predictive role and impact on different types of cancer (De Couck et al., 2018).

Several studies have identified factors contributing to increased psychological distress in cancer patients, including pre-operative anxiety, disease perception, depression, and low social support (Mohamed et al., 2023; Palapattu et al., 2004; Volz et al., 2022; Trudel and Maciejewski, 2021; Zhang et al., 2020). Reducing psychological distress, as well as addressing impairments in immune-inflammatory regulation, sympathetic nervous system activity, and hypothalamic-pituitary-adrenal axis dysregulation through stress-management interventions, has been associated with improved patient outcomes and increased survival (Spiegel, 2012). The vagus nerve, by enhancing adaptive emotion regulation and stress resilience, positively influences quality of life, reduces stress responses, and helps maintain immune signalling homeostasis by its regulation of

inflammation (De Couck et al., 2018; Pavlov and Tracey, 2012; Vanderhasselt and Ottaviani, 2022; Thayer et al., 2009). Beyond its predictive value, the vagus nerve may also offer a protective role against the progression of various diseases, including cancer, mostly due to its immune-regulatory effects (De Couck et al., 2018).

4.1. Limitations and future directions

Our study has several limitations that need to be acknowledged. The cross-sectional nature of our study limits our ability to draw causal inferences and even inferences about the direction of correlations. Longitudinal studies are necessary to clarify the directionality and experimental intervention studies are needed to establish causality between stress, life satisfaction, HRV, and inflammatory markers in cancer. Our sample size was relatively small, which may affect the generalizability of our findings and the statistical significance. Larger studies are needed to confirm these results and to explore potential variations across different populations. The use of self-reported questionnaires for assessing perceived stress and life satisfaction may introduce response biases. Assessing biomarkers and HRV at a single time point may not capture the dynamic nature of these physiological processes. Repeated measures over time would provide a more comprehensive understanding of their immune-regulatory effects in the context of cancer and distress.

5. Conclusion

Our study highlights the complex interplay between perceived stress, life satisfaction, inflammatory markers, and vagal activity in patients with bladder cancer. We found that perceived stress positively correlated with TNF-α and negatively with TGF-β levels only in patients with low HRV, suggesting that stress-related reduction in TGF-β could lead to increased inflammation, reduced immune regulation and potentially adverse cancer dynamics when HRV is low. Conversely, higher life satisfaction was positively correlated with TGF-β levels, indicating a better-regulated immune response in individuals with higher life satisfaction. These findings suggest that high vagal activity may buffer the effects of psychological distress on inflammatory processes, potentially reducing the risk of adverse cancer outcomes in patients with high vagal activity. Future research should aim to replicate these findings in larger, more diverse populations and employ longitudinal and experimental designs to establish causality. Incorporating objective measures of stress and well-being, along with biomarker assessments, will enhance our understanding of the mechanisms underlying these associations. This improved understanding could inform interventions aimed at reducing stress and improving life satisfaction, thereby mitigating inflammation and immune dysregulation and ultimately improving outcomes and clinical care for cancer patients.

CRediT authorship contribution statement

Iveta Mikolaskova: Writing – original draft, Investigation, Data curation. **Yori Gidron:** Writing – review & editing, Formal analysis, Conceptualization. **Vladimira Durmanova:** Investigation. **Magda Suchankova:** Investigation. **Maria Bucova:** Writing – review & editing, Supervision, Conceptualization. **Luba Hunakova:** Writing – review & editing, Supervision, Funding acquisition.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Luba Hunakova (a corresponding author) reports funding support by the Slovak Research and Development Agency (grant number APVV-22-0231) and the Scientific Grant Agency of the Ministry of Education, Science, Research and Sport of the Slovak Republic and Slovak Academy of Sciences (grant number VEGA 1/0090/22). The funding sources were not involved in the conduct of the research or preparation of the article.

Acknowledgments

Funding: The authors would like to thank the Scientific Grant Agency of the Ministry of Education, Science, Research and Sport of the Slovak Republic and Slovak Academy of Sciences, grant number VEGA 1/0090/22, and the Slovak Research and Development Agency, grant number APVV-22-0231, for their support. The funding sources were not involved in the conduct of the research or preparation of the article.

Data availability

Data will be made available on request.

References

Antoni, M.H., Dhabhar, F.S., 2019. The impact of psychosocial stress and stress management on immune responses in patients with cancer. Cancer 125 (9), 1417–1431. https://doi.org/10.1002/cncr.31943.

Arnsten, A.F., Raskind, M.A., Taylor, F.B., Connor, D.F., 2015. The effects of stress exposure on prefrontal cortex: translating basic research into successful treatments for post-traumatic stress disorder. Neurobiol. Stress 1, 89–99. https://doi.org/10.1016/j.ynstr.2014.10.002.

Atar, O., Ram, R., Avivi, I., et al., 2023. Vagal nerve activity predicts prognosis in diffused large B-cell lymphoma and multiple myeloma. J. Clin. Med. 12 (3), 908. https://doi.org/10.3390/jcm12030908.

Balkwill, F., Mantovani, A., 2001. Inflammation and cancer: back to Virchow? Lancet 357 (9255), 539–545. https://doi.org/10.1016/S0140-6736(00)04046-0.

Batlle, E., Massagué, J., 2019. Transforming growth factor-β signaling in immunity and cancer. Immunity 50 (4), 924–940. https://doi.org/10.1016/j.immuni.2019.03.024.

Batty, G.D., Russ, T.C., Stamatakis, E., Kivimäki, M., 2017. Psychological distress in relation to site-specific cancer mortality: pooling of unpublished data from 16 prospective cohort studies. BMJ 356, j108. https://doi.org/10.1136/bmj.j108.

Bonaz, B., Sinniger, V., Pellissier, S., 2016. Anti-inflammatory properties of the vagus nerve: potential therapeutic implications of vagus nerve stimulation. J. Physiol. 594 (20), 5781–5790. https://doi.org/10.1113/JP271539.

Bray, F., Laversanne, M., Sung, H., et al., 2024. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J. Clin. 74 (3), 229–263. https://doi.org/10.3322/caac.21834.

Brown, L.C., Murphy, A.R., Lalonde, C.S., Subhedar, P.D., Miller, A.H., Stevens, J.S., 2020. Posttraumatic stress disorder and breast cancer: risk factors and the role of inflammation and endocrine function. Cancer 126 (14), 3181–3191. https://doi.org/10.1002/cncr.32934.

Cai, Y., Zhaoxiong, Y., Zhu, W., Wang, H., 2024. Association between sleep duration, depression and breast cancer in the United States: a national health and nutrition examination survey analysis 2009-2018. Ann. Med. 56 (1), 2314235. https://doi.org/10.1080/07853890.2024.2314235.

Cain, D.W., Cidlowski, J.A., 2017. Immune regulation by glucocorticoids. Nat. Rev. Immunol. 17 (4), 233–247. https://doi.org/10.1038/nri.2017.1.

Chen, Z., He, S., Zhan, Y., He, A., Fang, D., Gong, Y., Li, X., Zhou, L., 2019. TGF-β-induced transgelin promotes bladder cancer metastasis by regulating epithelial-mesenchymal transition and invadopodia formation. EBioMedicine 47, 208–220. https://doi.org/10.1016/j.ebiom.2019.08.012.

Chida, Y., Hamer, M., Wardle, J., Steptoe, A., 2008. Do stress-related psychosocial factors contribute to cancer incidence and survival? Nat. Clin. Pract. Oncol. 5 (8), 466–475. https://doi.org/10.1038/ncponc1134.

Cohen, S., Kamarck, T., Mermelstein, R., 1994. Perceived stress scale. In: Cohen, S., Kessler, R.C., Gordon, L.U. (Eds.), Measuring Stress: A Guide for Health and Social Scientists, first ed. Oxford University Press, New York, NY, p. 10 https://www.scirp.org/reference/referencespapers?referenceid=3229612.

Cooper, T.M., McKinley, P.S., Seeman, T.E., Choo, T.H., Lee, S., Sloan, R.P., 2015. Heart rate variability predicts levels of inflammatory markers: evidence for the vagal anti-inflammatory pathway. Brain Behav. Immun. 49, 94–100. https://doi.org/10.1016/j.bbi.2014.12.017.

Dai, S., Mo, Y., Wang, Y., et al., 2020. Chronic stress promotes cancer development. Front. Oncol. 10, 1492. https://doi.org/10.3389/fonc.2020.01492.

David, C.J., Massagué, J., 2018. Contextual determinants of TGFβ action in development, immunity and cancer. Nat. Rev. Mol. Cell Biol. 19 (7), 419–435. https://doi.org/10.1038/s41580-018-0007-0.

De Couck, M., Caers, R., Spiegel, D., Gidron, Y., 2018. The role of the vagus nerve in cancer prognosis: a systematic and a comprehensive review. J Oncol 2018, 1236787. https://doi.org/10.1155/2018/1236787.

De Couck, M., Maréchal, R., Moorthamers, S., Van Laethem, J.L., Gidron, Y., 2016. Vagal nerve activity predicts overall survival in metastatic pancreatic cancer, mediated by inflammation. Cancer Epidemiol. 40, 47–51. https://doi.org/10.1016/j.canep.2015.11.007.

De Couck, M., Mravec, B., Gidron, Y., 2012. You may need the vagus nerve to understand pathophysiology and to treat diseases. Clin. Sci. 122 (7), 323–328. https://doi.org/10.1042/CS20110299.

De Couck, M., Gidron, Y., 2013. Norms of vagal nerve activity, indexed by Heart Rate Variability, in cancer patients. Cancer Epidemiol. 37 (5), 737–741. https://doi.org/10.1016/j.canep.2013.04.016.
Derynck, R., Turley, S.J., Akhurst, R.J., 2021. TGFβ biology in cancer progression and immunotherapy. Nat. Rev. Clin. Oncol. 18 (1), 9–34. https://doi.org/10.1038/s41571-020-0403-1.
Dunn, A.J., 2000. Cytokine activation of the HPA axis. Ann. N. Y. Acad. Sci. 917, 608–617. https://doi.org/10.1111/j.1749-6632.2000.tb05426.x.
Eckerling, A., Ricon-Becker, I., Sorski, L., Sandbank, E., Ben-Eliyahu, S., 2021. Stress and cancer: mechanisms, significance and future directions. Nat. Rev. Cancer 21 (12), 767–785. https://doi.org/10.1038/s41568-021-00395-5.
Elgellaie, A., Thomas, S.J., Kaelle, J., Bartschi, J., Larkin, T., 2023. Pro-inflammatory cytokines IL-1α, IL-6 and TNF-α in major depressive disorder: sex-specific associations with psychological symptoms. Eur. J. Neurosci. 57 (11), 1913–1928. https://doi.org/10.1111/ejn.15992.
Fahrenberg, J., Myrtek, M., Schumacher, J., Brähler, E., 2001. In: Life Satisfaction Questionnaire (LSQ), first ed. © Hogrefe-Verlag, Praha: Testcentrum. Göttingen, Bern, Toronto, Seattle, 2000.
Flint, M.S., Bovbjerg, D.H., 2012. DNA damage as a result of psychological stress: implications for breast cancer. Breast Cancer Res. 14 (5), 320. https://doi.org/10.1186/bcr3189.
Grivennikov, S.I., Greten, F.R., Karin, M., 2010. Immunity, inflammation, and cancer. Cell 140 (6), 883–899. https://doi.org/10.1016/j.cell.2010.01.025.
Haapakoski, R., Mathieu, J., Ebmeier, K.P., Alenius, H., Kivimäki, M., 2015. Cumulative meta-analysis of interleukins 6 and 1β, tumour necrosis factor α and C-reactive protein in patients with major depressive disorder. Brain Behav. Immun. 49, 206–215. https://doi.org/10.1016/j.bbi.2015.06.001.
Hamer, M., Chida, Y., Molloy, G.J., 2009. Psychological distress and cancer mortality. J. Psychosom. Res. 66 (3), 255–258. https://doi.org/10.1016/j.jpsychores.2008.11.002.
Hanahan, D., 2022. Hallmarks of cancer: new dimensions. Cancer Discov. 12 (1), 31–46. https://doi.org/10.1158/2159-8290.CD-21-1059.
Hunakova, L., Sabaka, P., Zvarik, M., Mikolaskova, I., Gidron, Y., Bucova, M., 2023. Linear and non-linear indices of vagal nerve in relation to sex and inflammation in patients with COVID-19. Biomed Rep 19 (5), 80. https://doi.org/10.3892/br.2023.1662.
Ironson, G., Banerjee, N., Fitch, C., Krause, N., 2018. Positive emotional well-being, health behaviors, and inflammation measured by C-Reactive protein. Soc. Sci. Med. 197, 235–243. https://doi.org/10.1016/j.socscimed.2017.06.020.
Jandackova, V.K., Jackowska, M., 2015. Low heart rate variability in unemployed men: the possible mediating effects of life satisfaction. Psychol. Health Med. 20 (5), 530–540. https://doi.org/10.1080/13548506.2014.987148.
Johnston, G.R., Webster, N.R., 2009. Cytokines and the immunomodulatory function of the vagus nerve. Br. J. Anaesth. 102 (4), 453–462. https://doi.org/10.1093/bja/aep037.
Kiecolt-Glaser, J.K., Gouin, J.P., Hantsoo, L., 2010. Close relationships, inflammation, and health. Neurosci. Biobehav. Rev. 35 (1), 33–38. https://doi.org/10.1016/j.neubiorev.2009.09.003.
Kim, H.G., Cheon, E.J., Bai, D.S., Lee, Y.H., Koo, B.H., 2018. Stress and heart rate variability: a meta-analysis and review of the literature. Psychiatry Investig 15 (3), 235–245. https://doi.org/10.30773/pi.2017.08.17.
King, M.L., 2019. The neural correlates of well-being: a systematic review of the human neuroimaging and neuropsychological literature. Cognit. Affect Behav. Neurosci. 19 (4), 779–796. https://doi.org/10.3758/s13415-019-00720-4.
Kluckova, K., Kozak, J., Szaboova, K., et al., 2020. TREM-1 and TREM-2 expression on blood monocytes could help predict survival in high-grade glioma patients. Mediat. Inflamm. 2020, 1798147. https://doi.org/10.1155/2020/1798147.
Lampert, R., Bremner, J.D., Su, S., et al., 2008. Decreased heart rate variability is associated with higher levels of inflammation in middle-aged men. Am. Heart J. 156 (4), 759.e1–759.e7. https://doi.org/10.1016/j.ahj.2008.07.009.
Larkin, K.T., Tiani, A.G., Brown, L.A., 2021. Cardiac vagal tone and stress. Neuroscience. https://doi.org/10.1093/acrefore/9780190264086.013.268.
Li, P., Hu, Y., Scelo, G., Myrskylä, M., Martikainen, P., 2023. Pre-existing psychological disorders, diabetes, and pancreatic cancer: a population-based study of 38,952 Finns. Cancer Epidemiol 82, 102307. https://doi.org/10.1016/j.canep.2022.102307.
Li, W.M., Wu, W.J., 2019. Transgelin in bladder cancer: a potential biomarker and therapeutic target. EBioMedicine 48, 16–17. https://doi.org/10.1016/j.ebiom.2019.09.011.
Liu, Y., Tian, S., Ning, B., Huang, T., Li, Y., Wei, Y., 2022. Stress and cancer: the mechanisms of immune dysregulation and management. Front. Immunol. 13, 1032294. https://doi.org/10.3389/fimmu.2022.1032294.
Liu, F.J., Wu, J., Gong, L.J., Yang, H.S., Chen, H., 2024. Non-invasive vagus nerve stimulation in anti-inflammatory therapy: mechanistic insights and future perspectives. Front. Neurosci. 18, 1490300. https://doi.org/10.3389/fnins.2024.1490300.
Makale, M.T., Kesari, S., Wrasidlo, W., 2017. The autonomic nervous system and cancer. Biocybern. Biomed. Eng. 37 (3), 443–452. https://doi.org/10.1016/j.bbe.2017.05.001.
Marsland, A.L., Gianaros, P.J., Prather, A.A., Jennings, J.R., Neumann, S.A., Manuck, S. B., 2007. Stimulated production of proinflammatory cytokines covaries inversely with heart rate variability. Psychosom. Med. 69 (8), 709–716. https://doi.org/10.1097/PSY.0b013e3181576118.
Martínez-Limón, A., Joaquin, M., Caballero, M., Posas, F., de Nadal, E., 2020. The p38 pathway: from biology to cancer therapy. Int. J. Mol. Sci. 21 (6), 1913. https://doi.org/10.3390/ijms21061913.
Massagué, J., 2008. TGFbeta in cancer. Cell 134 (2), 215–230. https://doi.org/10.1016/j.cell.2008.07.001.
McFarland, D.C., Doherty, M., Atkinson, T.M., et al., 2022. Cancer-related inflammation and depressive symptoms: systematic review and meta-analysis. Cancer 128 (13), 2504–2519. https://doi.org/10.1002/cncr.34193.
Mehta, N.D., Stevens, J.S., Li, Z., Fani, N., Gillespie, C.F., Ravi, M., Michopoulos, V., Felger, J.C., 2022. Inflammation, amygdala-ventromedial prefrontal functional connectivity and symptoms of anxiety and PTSD in African American women recruited from an inner-city hospital: preliminary results. Brain Behav. Immun. 105, 122–130. https://doi.org/10.1016/j.bbi.2022.06.013.
Menard, C., Pfau, M.L., Hodes, G.E., et al., 2017. Social stress induces neurovascular pathology promoting depression. Nat. Neurosci. 20 (12), 1752–1760. https://doi.org/10.1038/s41593-017-0010-3.
Mercogliano, M.F., Bruni, S., Mauro, F., Elizalde, P.V., Schillaci, R., 2021. Harnessing tumor necrosis factor alpha to achieve effective cancer immunotherapy. Cancers 13 (3), 564. https://doi.org/10.3390/cancers13030564.
Mohamed, N.E., Leung, T.M., Benn, E.K., et al., 2023. Depression and anxiety among patients treated for bladder cancer: examining clinical, demographic, and psychosocial predictors. Am. J. Clin. Exp. Urology 11 (5), 401–413.
Ohira, H., Matsunaga, M., Osumi, T., et al., 2013. Vagal nerve activity as a moderator of brain-immune relationships. J. Neuroimmunol. 260 (1–2), 28–36. https://doi.org/10.1016/j.jneuroim.2013.04.011.
Palapattu, G.S., Haisfield-Wolfe, M.E., Walker, J.M., et al., 2004. Assessment of perioperative psychological distress in patients undergoing radical cystectomy for bladder cancer. J. Urol. 172 (5 Pt 1), 1814–1817. https://doi.org/10.1097/01.ju.0000141245.08456.1a.
Pavlov, V.A., Tracey, K.J., 2012. The vagus nerve and the inflammatory reflex—linking immunity and metabolism. Nat. Rev. Endocrinol. 8 (12), 743–754. https://doi.org/10.1038/nrendo.2012.189.
Pickup, M.W., Owens, P., Moses, H.L., 2017. TGF-B, bone morphogenetic protein, and activin signaling and the tumor microenvironment. Cold Spring Harbor Perspect. Biol. 9 (5), a022285. https://doi.org/10.1101/cshperspect.a022285.
Porges, S.W., 2007. The polyvagal perspective. Biol. Psychol. 74 (2), 116–143. https://doi.org/10.1016/j.biopsycho.2006.06.009.
Rosas-Ballina, M., Olofsson, P.S., Ochani, M., Valdés-Ferrer, S.I., Levine, Y.A., Reardon, C., Tusche, M.W., Pavlov, V.A., Andersson, U., Chavan, S., Mak, T.W., Tracey, K.J., 2011. Acetylcholine-synthesizing T cells relay neural signals in a vagus nerve circuit. Science (New York, N.Y.) 334 (6052), 98–101. https://doi.org/10.1126/science.1209985.
Rosella, L.C., Fu, L., Buajitti, E., Goel, V., 2019. Death and chronic disease risk associated with poor life satisfaction: a population-based cohort study. Am. J. Epidemiol. 188 (2), 323–331. https://doi.org/10.1093/aje/kwy245.
Roy, S., Roy, S., Rana, A., Akhter, Y., Hande, M.P., Banerjee, B., 2018. The role of p38 MAPK pathway in p53 compromised state and telomere mediated DNA damage response. Mutat. Res. Genet. Toxicol. Environ. Mutagen 836 (Pt A), 89–97. https://doi.org/10.1016/j.mrgentox.2018.05.018.
Sanjabi, S., Oh, S.A., Li, M.O., 2017. Regulation of the immune response by TGF-β: from conception to autoimmunity and infection. Cold Spring Harbor Perspect. Biol. 9 (6), a022236. https://doi.org/10.1101/cshperspect.a022236.
Shrout, M.R., Renna, M.E., Madison, A.A., et al., 2020. Relationship satisfaction predicts lower stress and inflammation in breast cancer survivors: a longitudinal study of within-person and between-person effects. Psychoneuroendocrinology 118, 104708. https://doi.org/10.1016/j.psyneuen.2020.104708.
Spiegel, D., 2012. Mind matters in cancer survival. Psychooncology 21 (6), 588–593. https://doi.org/10.1002/pon.3067.
Stolfi, C., Troncone, E., Marafini, I., Monteleone, G., 2020. Role of TGF-Beta and Smad7 in gut inflammation, fibrosis and cancer. Biomolecules 11 (1), 17. https://doi.org/10.3390/biom11010017.
Stojnev, S., Krstić, M., Čukuranović Kokoris, J., Conić, I., Petković, I., Ilić, S., Milosević-Stevanović, J., Veličković, L.J., 2019. Prognostic impact of canonical TGF-β signaling in urothelial bladder cancer. Medicina 55 (6), 302. https://doi.org/10.3390/medicina55060302.
Tauriello, D.V.F., Sancho, E., Batlle, E., 2022. Overcoming TGFβ-mediated immune evasion in cancer. Nat. Rev. Cancer 22 (1), 25–44. https://doi.org/10.1038/s41568-021-00413-6.
Thayer, J.F., Hansen, A.L., Saus-Rose, E., Johnsen, B.H., 2009. Heart rate variability, prefrontal neural function, and cognitive performance: the neurovisceral integration perspective on self-regulation, adaptation, and health. Ann. Behav. Med. 37 (2), 141–153. https://doi.org/10.1007/s12160-009-9101-z.
Tracey, K.J., 2002. The inflammatory reflex. Nature 420 (6917), 853–859. https://doi.org/10.1038/nature01321.
Trudel, J., Maciejewski, C., 2021. MP19-02 impaired emotional, physical, and social well-being in radical cystectomy patients. J. Urol. 206 (3S). https://doi.org/10.1097/JU.0000000000002004.02.
Tylutka, A., Walas, Ł., Zembron-Lacny, A., 2024. Level of IL-6, TNF, and IL-1β and age-related diseases: a systematic review and meta-analysis. Front. Immunol. 15, 1330386. https://doi.org/10.3389/fimmu.2024.1330386.
Van Esch, L., Roukema, J.A., Ernst, M.F., Nieuwenhuijzen, G.A., De Vries, J., 2012. Combined anxiety and depressive symptoms before diagnosis of breast cancer. J. Affect. Disord. 136 (3), 895–901. https://doi.org/10.1016/j.jad.2011.09.012.
Vanderhasselt, M.A., Ottaviani, C., 2022. Combining top-down and bottom-up interventions targeting the vagus nerve to increase resilience. Neurosci. Biobehav. Rev. 132, 725–729. https://doi.org/10.1016/j.neubiorev.2021.11.018.
Vine, M.F., Calingaert, B., Berchuck, A., Schildkraut, J.M., 2003. Characterization of prediagnostic symptoms among primary epithelial ovarian cancer cases and controls. Gynecol. Oncol. 90 (1), 75–82. https://doi.org/10.1016/s0090-8258(03)00175-6.

Volz, Y., Troost, J., Eismann, L., et al., 2022. The burden of fear of cancer recurrence in genitourinary cancers: a prospective study (NCT04535921). Oncol. Res. Treat. 45 (12), 744–751. https://doi.org/10.1159/000527161.

Wang, C., Shen, Y., Ni, J., Hu, W., Yang, Y., 2022. Effect of chronic stress on tumorigenesis and development. Cell. Mol. Life Sci. 79 (9), 485. https://doi.org/10.1007/s00018-022-04455-3.

Wéber, A., Vignat, J., Shah, R., et al., 2024. Global burden of bladder cancer mortality in 2020 and 2040 according to GLOBOCAN estimates. World J. Urol. 42 (1), 237. https://doi.org/10.1007/s00345-024-04949-8.

Weber, C.S., Thayer, J.F., Rudat, M., Wirtz, P.H., Zimmermann-Viehoff, F., Thomas, A., Perschel, F.H., Arck, P.C., Deter, H.C., 2010. Low vagal tone is associated with impaired post stress recovery of cardiovascular, endocrine, and immune markers. Eur. J. Appl. Physiol. 109 (2), 201–211. https://doi.org/10.1007/s00421-009-1341-x.

Yao, D., Dong, M., Dai, C., Wu, S., 2019. Inflammation and inflammatory cytokines contribute to the initiation and development of ulcerative colitis and its associated cancer. Inflamm. Bowel Dis. 25 (10), 1595–1602. https://doi.org/10.1093/ibd/izz149.

Yoshimura, A., Wakabayashi, Y., Mori, T., 2010. Cellular and molecular basis for the regulation of inflammation by TGF-beta. J. Biochem. 147 (6), 781–792. https://doi.org/10.1093/jb/mvq043.

Zhang, H., Caudle, Y., Wheeler, C., Zhou, Y., Stuart, C., Yao, B., Yin, D., 2018. TGF-β1/Smad2/3/Foxp3 signaling is required for chronic stress-induced immune suppression. J. Neuroimmunol. 314, 30–41. https://doi.org/10.1016/j.jneuroim.2017.11.005.

Zhang, Z., Yang, L., Xie, D., et al., 2020. Illness perceptions are a potential predictor of psychological distress in patients with non-muscle-invasive bladder cancer: a 12-month prospective, longitudinal, observational study. Psychol. Health Med. 25 (8), 969–979. https://doi.org/10.1080/13548506.2019.1707242.

Zhang, X., Zhang, Y., He, Z., et al., 2019. Chronic stress promotes gastric cancer progression and metastasis: an essential role for ADRB2. Cell Death Dis. 10 (11), 788. https://doi.org/10.1038/s41419-019-2030-2.

Zhou, M., Aziz, M., Ochani, M., Wang, P., 2020. Correction of immunosuppression in aged septic rats by human ghrelin and growth hormone through the vagus nerve-dependent inhibition of TGF-β production. Mol. Med. 26 (1), 71. https://doi.org/10.1186/s10020-020-00195-x.

Zhou, X., Ma, Z., Zhang, L., et al., 2016. Heart rate variability in the prediction of survival in patients with cancer: a systematic review and meta-analysis. J. Psychosom. Res. 89, 20–25. https://doi.org/10.1016/j.jpsychores.2016.08.004.