Cancer-Related Fatigue

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LYMPHOMA COALITION

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OVERVIEW

Cancer-related fatigue (CRF) is one of the most prevalent and distressing symptoms experienced by patients with cancer during and after therapy.[1,2] It can intensify the experience of other disease symptoms, interfere with the ability to carry out everyday activities, and negatively impact quality of life.[2]

Fatigue is in fact the leading physical symptom affecting quality of life reported by respondents to the Lymphoma Coalition 2018 Global Patient Survey on Lymphomas and CLL (LC 2018 GPS), regardless of whether the patient is newly diagnosed, in treatment, has relapsed disease or is in remission.

CRF is multidimensional, has multiple causes and is experienced differently by each individual.[3] As such, the healthcare community has struggled to define CRF and develop effective screening, assessment and treatment protocols. This has created barriers in doctor-patient communication concerning fatigue, and has led to the continued underreporting, under diagnosis, and under treatment of CRF.[4]

Due to advances in cancer detection and treatment, healthcare professionals (HCPs) are now likely to see patients with prolonged states of fatigue extending months to years beyond treatment completion.[5,6,7] This underscores the need to address fatigue as a significant diagnosis when treating patients with, and survivors of cancer. Fatigue management needs to be an integral part of total healthcare and greater attention, collaboration, and communication is still required in this area.

This report will cover:

- Defining CRF;
- Understanding the causes of CRF;
- The effects of CRF on patients and survivors; and
- CRF screening, evaluation and treatment.

Words highlighted in **bold** are defined in the glossary at the end of the report.

WHAT IS CANCER-RELATED FATIGUE (CRF)?

Cancer-related fatigue (CRF) is different from the fatigue of daily life; it is more severe, more distressing, and less likely to be relieved by rest.[5] There is no universally agreed upon definition of CRF across scientific and healthcare communities.[6] However, the definition proposed by the National Comprehensive Cancer Network (NCCN) remains the most commonly cited:

'Cancer-related fatigue is a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning'.[8]

CRF often comes suddenly without warning and is usually not a result of exertion.[8] Some describe CRF as feeling weak, drained, or 'washed out'.[9] The severe exhaustion often dominates the everyday life of affected patients and survivors of cancer.[4] For example, those affected by CRF may feel too tired to eat, walk to the bathroom, or even use the TV remote. It can be difficult to think or move.[9]

The following are signs of CRF[9]:

- Feeling tired and it does not get better with sleep or rest, it keeps coming back, or it becomes severe.
- Feeling more tired than usual during or after activity.
- Feeling tired and it is not related to an activity.
- Arms and legs feel heavy and hard to move.
- Having no energy and/or feeling weak.
- Spending more time in bed and/or sleeping more. Or, having trouble sleeping.
- Having trouble concentrating or becoming confused.
- Experiencing tiredness that disrupts work, social life, or daily routine.

Prevalence

Fatigue is one of the most common symptoms that patients with cancer experience; estimated prevalence rates range from 40%-90% among published scientific studies.[3-4,6,8,10-11] The LC 2018 GPS indicated that 72% of patients with lymphoma reported experiencing life-impacting fatigue.

The variation in prevalence rates among populations of patients with cancer may be partially dependent on the type and stage of cancer, the type of treatment, and how the fatigue is measured.[3,6] The LC 2018 GPS showed that fatigue prevalence varied according to both lymphoma subtype (table 1) as well as stage of the patient experience (table 2).

Table 1. Prevalence of fatigue affecting well-being by lymphoma subtype

Lymphoma Subtype	Patient %
Transformed*	94
Waldenstrom's Macroglobulinaemia	80
Burkitt's	79
Peripheral T-Cell	72
Diffuse Large B-Cell (DLBCL) (if not told what specific type)	72
Hodgkin	72
Chronic Lymphocytic Leukaemia (CLL)/ Small Lymphocytic Lymphoma (SLL)	71
Follicular	71
Mantle Cell	71
Anaplastic Large Cell	68

Mucosa-Associated Lymphoid Tissue (MALT)/Marginal Zone	67
Diffuse Large B-Cell (DLBCL) Germinal Centre B-Cell (GCB)	65
Cutaneous	65
Extranodal Killer T-cell	64
Diffuse Large B-Cell (DLBCL) Activated B-Cell (ABC)	61

**Transformed was asked as both a subtype, as well as a stage of patient experience (table 2 below).*

Table 2. Prevalence of fatigue affecting well-being by stage of patient experience

Stage of Patient Experience	Patient %
Newly diagnosed	59
Newly diagnosed and currently in treatment	69
Watch and wait	58
In remission and treatment free for ≤ 2 years	76
In remission and treatment free for 2-5 years	75
In remission and treatment free for +5 years	77
Relapsed 1 time and currently in treatment	78
Relapsed 2+ times and currently in remission	74
Relapsed 2+ times and currently in treatment	82
Finished treatment and in maintenance therapy	68
Transformed*	79

**Transformed was asked as both a stage of patient experience, as well as a subtype (table 1 above).*

How Long Does CRF Last?

Fatigue occurs before and during a lymphoma diagnosis, as well as during treatment and throughout the survival trajectory.[6] HCPs are now likely to see patients with prolonged states of fatigue related to chronic cancers, extended palliative phases, and the late effects of treatment.[3,5,11] This is reflected in research as many survivors of cancer report that fatigue remains a relevant problem months or even years after treatment ends.[4,6,12]

According to the LC 2018 GPS, increasing numbers of patients experienced life-impacting fatigue as they moved along their disease course (table 2). Prevalence of fatigue was highest in the later stages of relapse, remission, and disease transformation, indicating fatigue may be getting worse rather than better over time. Further, some patients with lymphoma reported experiencing fatigue for up to 8+ years following treatment (figure 1). To examine the persistence of fatigue more precisely, a subset of patients (from the LC 2018 GPS) who were diagnosed prior to 2012 were analysed (figure 2). The long-term impact of fatigue was particularly evident in this patient group as 25% reported experiencing fatigue for 8+ years following treatment.

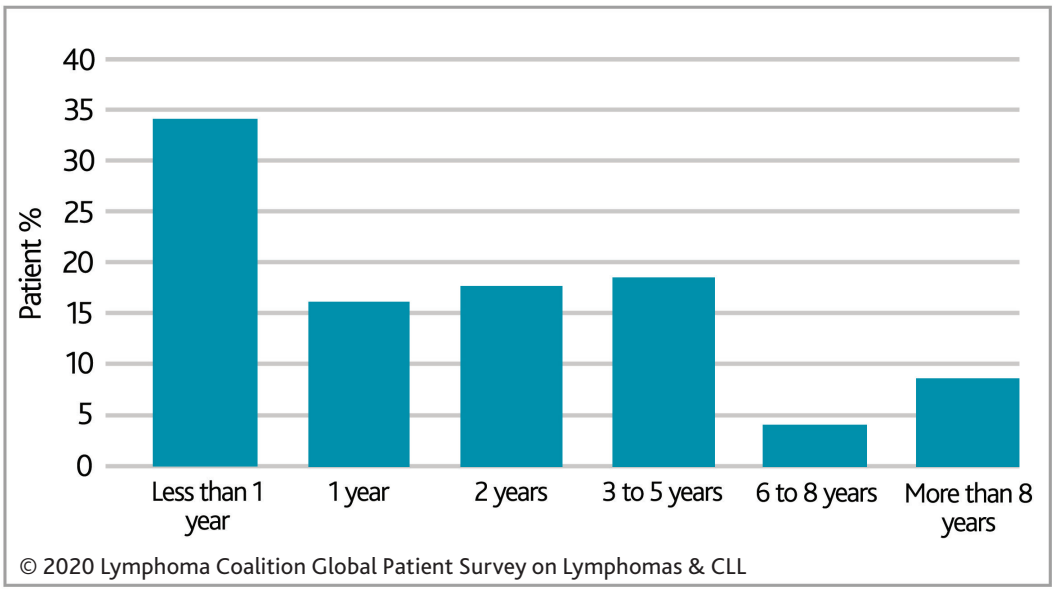

Figure 1. How long fatigue lasted following treatment completion among patients with lymphoma who reported experiencing life-impacting fatigue

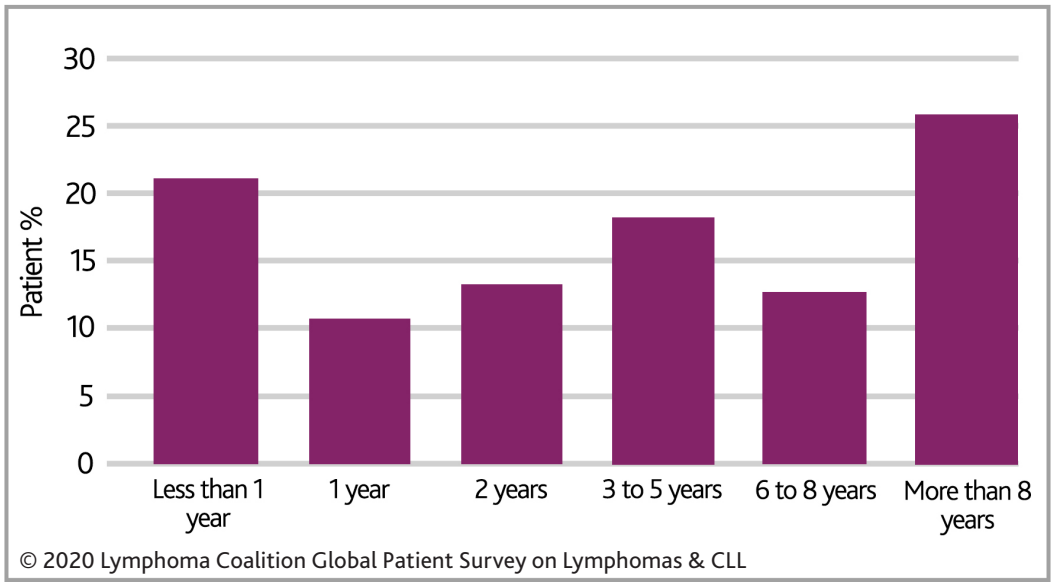

Figure 2. How long fatigue lasted following treatment completion among patients with lymphoma diagnosed prior to 2012 who reported experiencing life-impacting fatigue

WHAT CAUSES CRF?

Despite the prevalence of CRF among patients with, and survivors of cancer, the causes are still not fully understood.[13] Understanding the **aetiology** is complicated as CRF is a symptom of cancer itself, as well as a side effect of many of the therapies used to treat it. Further, CRF can be influenced by individual patient-related factors.[8,14-15] It is imperative that understanding of CRF causes be improved in order to identify targets to develop therapies that reduce CRF burden.[14]

A diagrammatic representation of CRF causes, as understood by research to date, is depicted in figure 3 and explained in detail below.

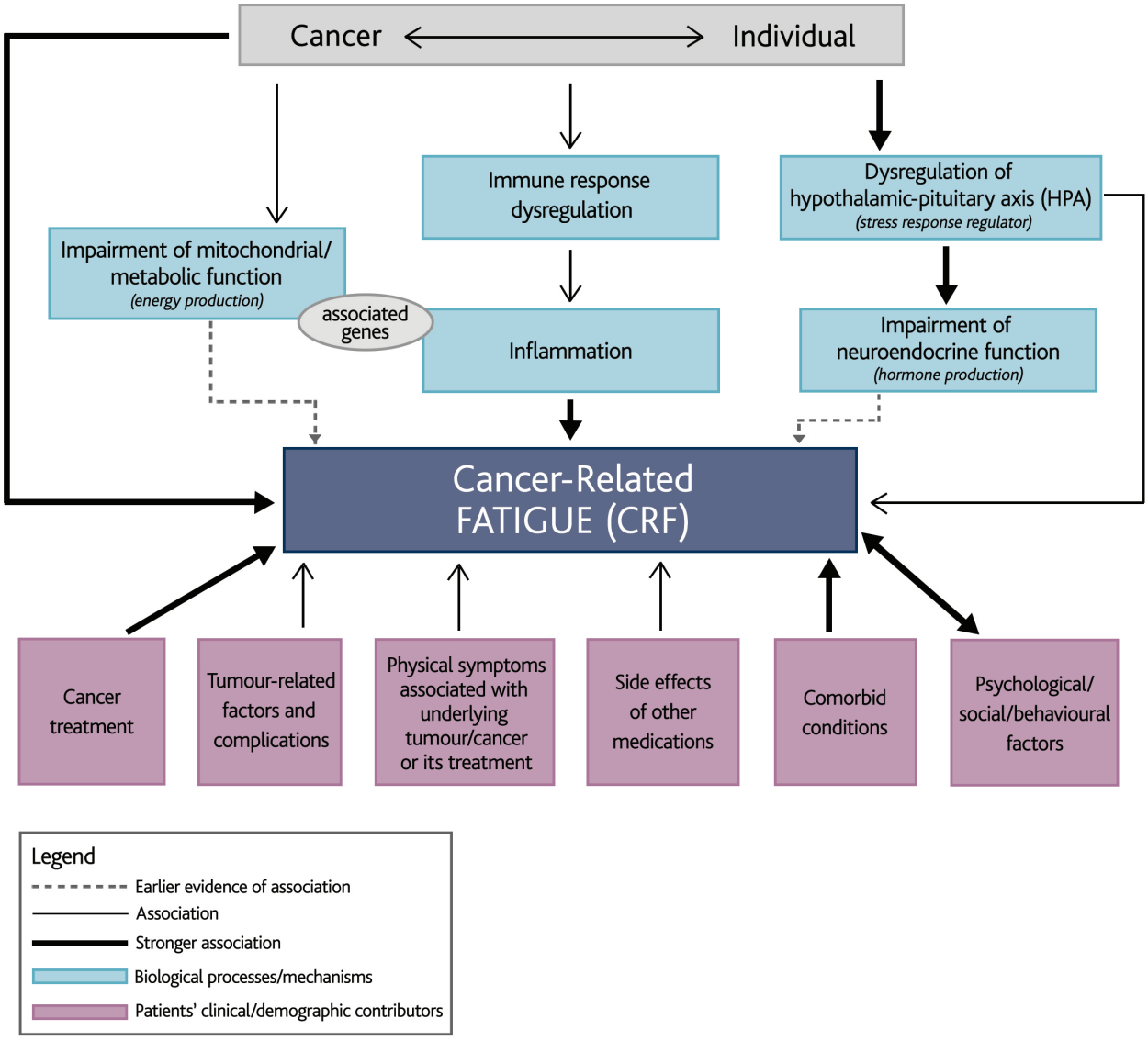

Figure 3. Known causes of CRF (biological and patient-related clinical/demographic) as proven through evidence-based research

Biological Causes (figure 3 blue boxes)

The biology and the specific mechanisms involved in the **pathophysiology** of CRF are complex, and studies suggest that CRF is a result of multiple biological processes. There are several pathways that could contribute to the disruption of normal **neuronal** (nerve cell) **function** and result in the symptom of CRF. These pathways include chronic inflammation, **autonomic imbalance**, **circadian rhythm** dysregulation, **hypothalamic-pituitary-adrenal (HPA) axis** (stress response) dysregulation, and/or **mitochondrial** damage.[13-14] Genetic factors have been reported to influence these biological processes.[13-14]

The proposed interaction(s) of these biological processes is as follows[13-14]:

- Cancer and its treatment can lead to immune activation with a release of **pro-inflammatory cytokines**. These cytokines cause peripheral inflammation.
- The pro-inflammatory cytokine release and immune cell activation triggers a series of events which includes alterations in endocrine functions (hormone production), HPA axis dysfunction (stress response regulator), and mitochondrial impairment in the central nervous system and in the periphery (metabolic regulation/energy production).
- This series of events translates into skeletal muscle dysfunction (body movement and support), and the experience of symptoms including fatigue, depression, sleep disturbance, and cognitive impairments.

For details on the possible biomarkers involved in each step of this cascade, please see Appendix 1.

Patient Factors (figure 3 purple boxes)

As was explained above, cancer and/or its treatment induce a cascade of biological changes leading to CRF. However, there are other factors that can influence these series of events. An individual patient's clinical and demographic characteristics can contribute to these biological processes, serving to better or worsen the symptom of CRF.[8,14-15] For example, patients who are older, who have an advanced stage cancer, or who have had more than one type of treatment are more likely to experience long-term fatigue.[16] Many people also have medical problems, illnesses, or take medications that are unrelated to cancer but may add to their fatigue.

Some of the most commonly cited fatigue-compounding causes are outlined below:

1. **Iatrogenic factors** related to cancer treatment[3,8,12,15]:	2. Tumour-related factors and complications[8-9,15,17]:
» Chemotherapy » Immunotherapy » Radiotherapy » Surgery » Hormonal therapies » Small-molecule targeted therapies	» Anaemia » Dehydration » Anorexia » Thrombosis (blood clots)/pulmonary embolism » Kidney, liver or heart failure » Neurological deficit » Fever
3. Physical symptoms associated with the underlying tumour/cancer or its treatment[3,8-9,15,17]:	**4. Side effects of other medication[3,8-9,15,17]:**
» Pain » Dyspnoea (difficulty breathing) » Difficulty swallowing » Appetite loss	» Opioids (pain medications) » Psychiatric drugs » Antihistamines » Beta blockers » Corticosteroids » Antidepressant drugs » Anti-nausea medicines » Anti-seizure medications
5. Comorbid conditions[3,8,15,17]:	**6. Psychological/social/behavioural factors[3,8-9,15]:**
» Hypothyroidism » Chronic obstructive pulmonary disease (COPD) » Diabetes mellitus » Cardiovascular disease » Infections	» Anxiety » Fear of cancer recurrence » Depression » Emotional distress » Sleep disorder » Decreased physical activity, lack of exercise » Poor nutrition » Alcohol and other non-prescribed drugs

HOW DOES CRF AFFECT PATIENTS AND SURVIVORS?

CRF greatly affects patients' quality of life, physically, mentally, emotionally and socially. Studies indicate that patients often perceive fatigue to be the most distressing symptom associated with cancer and its treatment.[5,18] More distressing than pain or nausea/vomiting, which can generally be managed with medications.[5,18] This was reflected in LC 2018 GPS data, where respondents rated fatigue as the physical side effect with the greatest impact on quality of life.

As is depicted in figure 3, psychological, social and behavioural factors (listed in #6 above) function in what can become a vicious cause-and-effect cycle with CRF. CRF can be caused by, as well as perpetuate the presence and severity of various negative psychological, social, and behavioural factors.

Persistent CRF affects quality of life as individuals begin to experience social invalidation and de-moralisation.[2-3,5,18] This means that they become too exhausted to fully participate in the roles and activities that make their life meaningful. For example, patients may not be able to return to work or have to work fewer hours, which can affect their financial status.[3-4,8] They may have to play a new or different role in their family and their relationships, or relationships may begin to deteriorate altogether.[3-4,8] They may have to withdraw from activities they previously enjoyed, or their functional status may be so diminished that they experience difficulty performing activities of daily living.[2-3,8,12]

The presence of one or many of these factors can contribute to the development of, or intensify existing psychological problems like anxiety, depression, sleep disorders, cognitive disorders, and emotional distress.[3,8,15] These psychological issues can then reflect back negatively on the social and behavioural factors. All of this can serve to increase the severity of fatigue as a symptom, which can reduce a patient's ability to complete medical treatments, and/or interfere with a patient's motivation to fight their disease.[1,3]

The LC 2018 GPS indicated that as a result of fatigue, patients with lymphoma had experienced changes in several areas of life (figure 4). Most commonly, patients reported that their general activity levels (78%) and their lifestyle (72%) had changed. Additionally, 62% of patients reported that fatigue affected their ability to work.

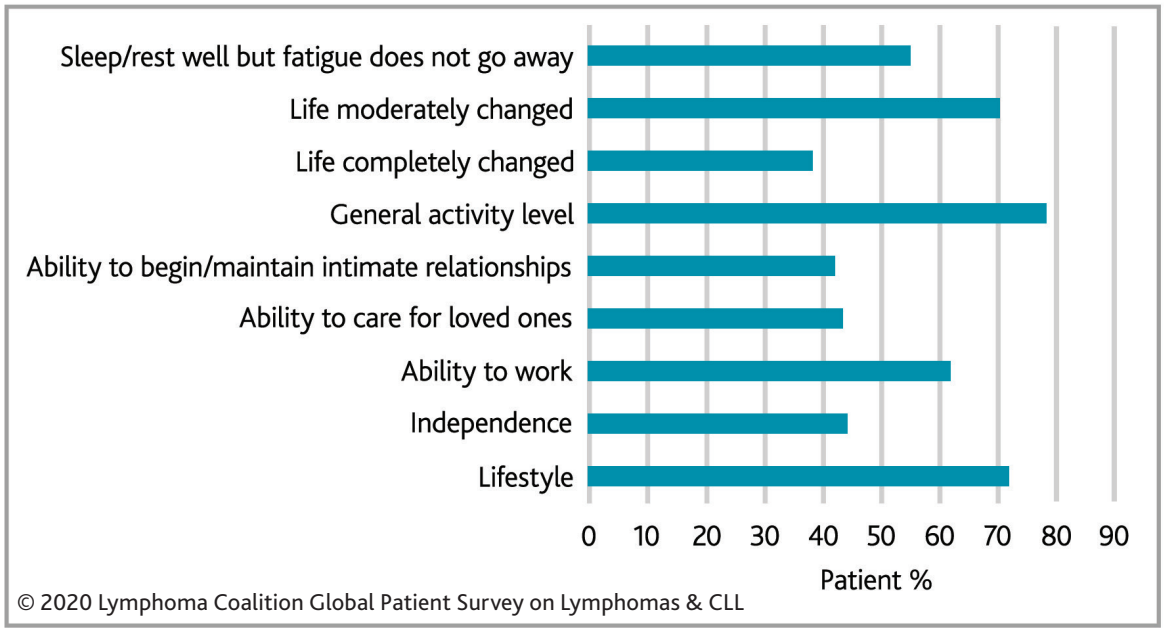

Figure 4. Life changes experienced by patients with lymphoma as a result of fatigue

The LC 2018 GPS indicated that fatigue was associated with psychosocial issues as well. Compared to patients who did not experience fatigue, the reported prevalence of every psychosocial issue was higher for patients with fatigue (figures 5 & 6). This was true both during and after treatment.

Patients with fatigue particularly reported experiencing changes in relationships with their loved ones, friends or co-workers/social life both during (35%) and after (24%) treatment. Patients with fatigue also reported experiencing anxiety (30% during treatment, 21% after), stress related to finances (28% during, 20% after), concerns about body image (26% during, 18% after), and fear of cancer relapse (25% during, 37% after).

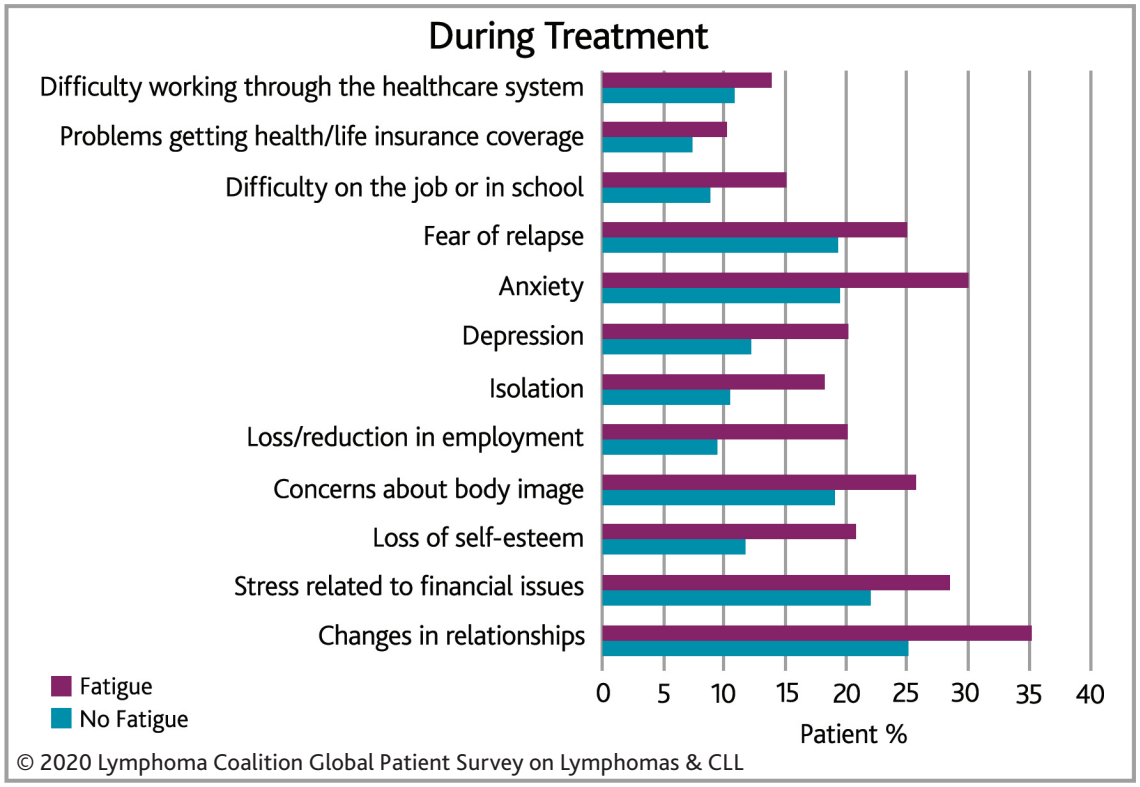

Figure 5. Psychosocial issues affecting wellbeing *during* treatment amongst patients with lymphoma with and without fatigue

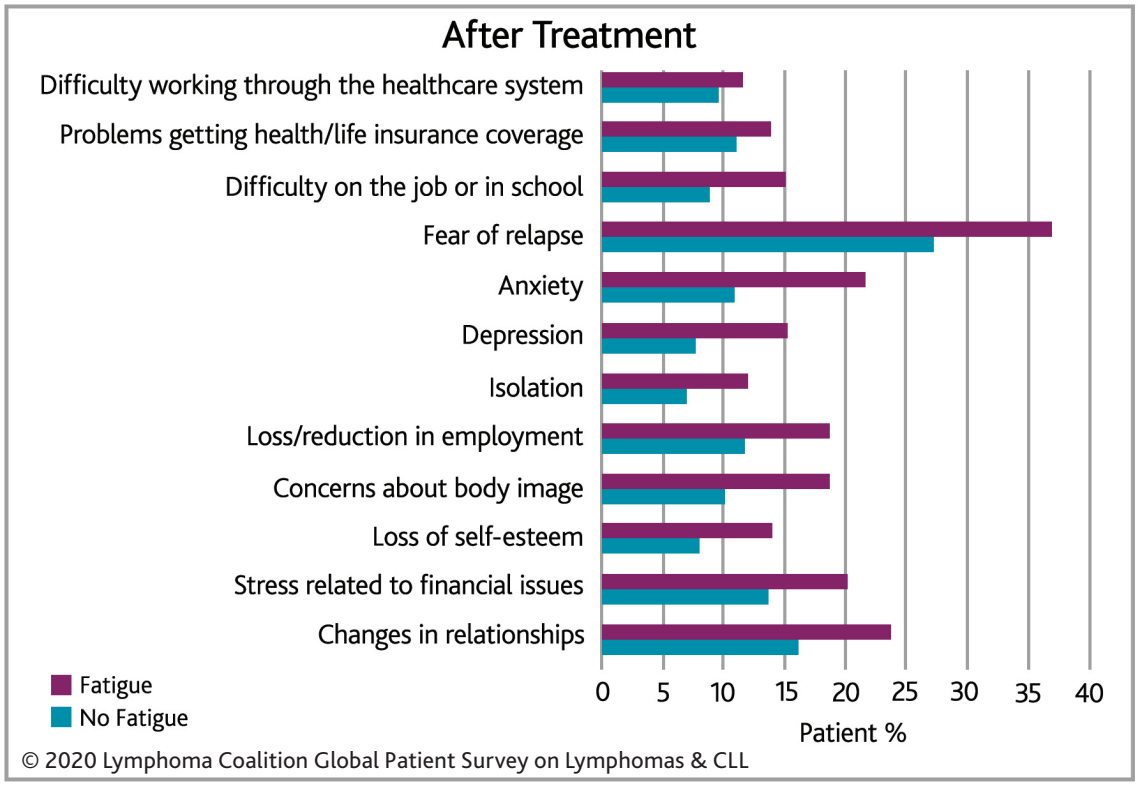

Figure 6. Psychosocial issues affecting wellbeing *after* treatment amongst patients with lymphoma with and without fatigue

CRF SCREENING, EVALUATION AND TREATMENT

Fatigue in patients with cancer continues to be underreported, underdiagnosed, and undertreated.[5,16] This can negatively impact treatment adherence, disease control, and patient outcomes.[14]

HCPs have been challenged in their efforts to assess and help their patients manage CRF because of various patient-related, professional, and systematic barriers.[3,5] For example, studies have revealed that patients fail to report fatigue for several reasons, including a belief that fatigue is inevitable, scientifically unmeasurable, untreatable, and unimportant.[3,16] Patients may also fear that reporting CRF will negatively affect their medical treatment, such as needing to reduce or stop treatment.[3]

HCPs may not initiate a discussion about CRF if they do not recognise it is an issue for the patient. HCPs may also lack knowledge about the underlying causes of fatigue or be unaware that there are effective treatments for fatigue.[3] Screening for CRF is not currently systematic or effective in many clinical settings.[8] Additionally, documentation of CRF in medical records is not widespread common practice.[3] As a result, CRF assessment and management have not been made priorities, and the symptom continues to go unrecognised and untreated.[3,14]

Despite these barriers, multiple programs have been initiated by different organisations to define CRF and fund research activities related to its aetiology.[14] Research has begun to document the incidence and prevalence of CRF, as well as correlate this data with the degree of disruption to patient quality of life.[5] Additionally, the National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology (ESMO) have developed clinical practice guidelines for CRF.

Both sets of clinical practice guidelines have 4 defined phases[5,19,20]:

1. Screening
2. Primary evaluation (NCCN) or diagnostic assessment (ESMO)
3. Intervention (NCCN) or management (ESMO)
4. Re-evaluation

Both contain similar recommendations regarding CRF care.

1. Screening

From the point of diagnosis onward, the HCP must screen every patient with, and survivor of cancer for fatigue presence and severity.[5,19,20] It is important to note that screening is not a one-time experience, but should be conducted at regular intervals during therapy and aftercare if clinically indicated.[20] If fatigue is detected, the severity must be assessed using a **quantitative**, or semi-quantitative measurement tool.[5,19,20] Since fatigue is a subjective experience, these measurement tools rely on patients' ability to accurately self-report. A simple 0 (no fatigue) to 10 (worst fatigue imaginable) numeric rating scale can be used, with established cut-off values for severity. A score

of 1-3 indicates mild fatigue, 4-6 moderate fatigue, and 7-10 severe fatigue.[5,19,20] If patients cannot put a number to their fatigue, they can explain it as 'mild', 'moderate' or 'severe'. This scale can also be adjusted according to age; for children (age 7-12) it can be simplified to a 1-5 scale, and for young children (age <5-6) simplified even further to 'tired' or 'not tired'.[5]

Beyond this recommended methodology, there are many valid and reliable instruments available to assess fatigue (see Appendix 2). There are both unidimensional and multidimensional measurement scales. A recent systematic review (77 studies)[6] conducted a quality assessment to evaluate the **psychometric properties** of scales to measure CRF in patients. Four scales met the most quality assessment criteria; two were unidimensional and two were multidimensional. The unidimensional scales were the Brief Fatigue Inventory (BFI) and the Functional Assessment of Chronic Therapy-Fatigue (FACT-F), and the multidimensional scales were the Multidimensional Fatigue Inventory (MFI-20) and the Piper Fatigue Scale-Revised (PFS-R).[6] Consideration must be given when choosing the appropriate scale, both for clinical and research purposes, as each scale measures different aspects of CRF.

Essential to the screening phase is patients' willingness to speak up about their fatigue. The LC 2018 GPS found less than 20% of patients with fatigue spoke to their doctor about how fatigue was impacting their life (see figure 7 below for detailed information). Though fatigue is a common symptom for patients with and survivors of cancer, it must not be assumed to be an unavoidable part of their disease experience. Treating fatigue is an important part of care for the patient and their family and it is often possible to lessen fatigue. However, before anything can be done to help the patient, the cancer care team must know about their level and severity of fatigue.[8,12,17]

If, using any CRF-measurement scale, fatigue is determined to be absent or mild, the patient and their family should receive education and common management strategies for fatigue[5,19] (see Interventions). Periodic re-screening and re-evaluation are recommended.[5,19,20] If fatigue is rated moderate to severe (values of 4 or higher out of 10), a more in-depth primary evaluation should be conducted to identify treatable contributing factors and comorbid conditions.[5,19,20]

2. Primary Evaluation/Diagnostic Assessment

Patients identified as experiencing moderate to severe fatigue require a more focused fatigue history and physical examination as part of the primary evaluation/diagnostic assessment.[5,19,20] This may include a review of body systems and other physical, emotional, and cognitive symptoms. This should also include a review of different aspects of fatigue including onset, progression, patterns, associated alleviating factors, and interference with function.[5,19,20] These aspects of fatigue are documented using patient self-assessment and reporting, making patient communication very important. However, the LC 2018 GPS indicated that while fatigue had many effects on patients' normal functioning, very few patients discussed these effects with the doctor (figure 7).

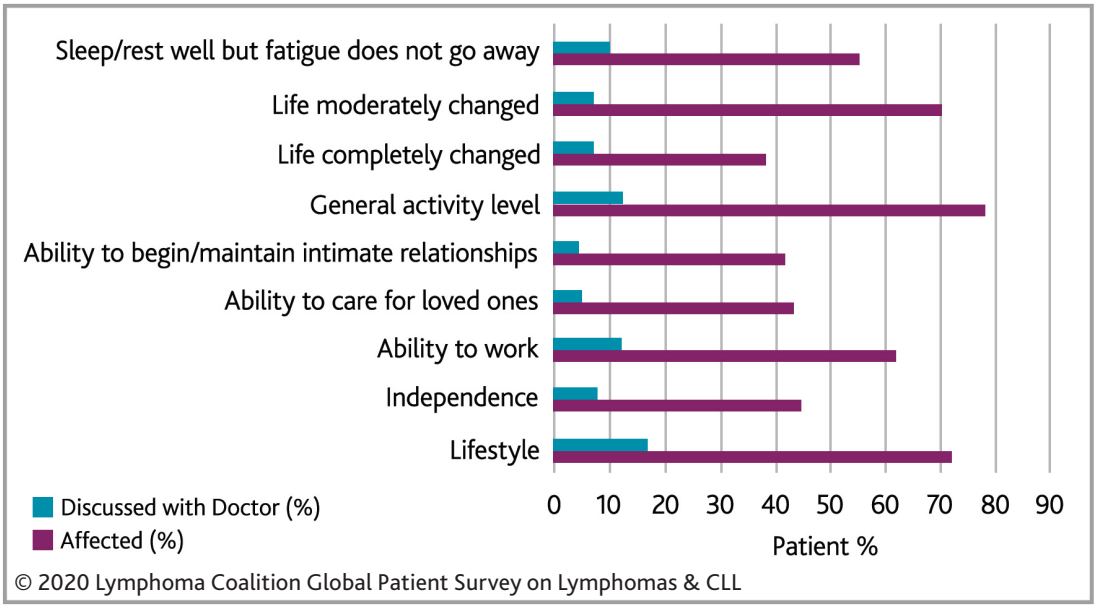

Figure 7. Life changes experienced by patients with lymphoma as a result of fatigue, and discussion of these changes with the doctor

This phase also includes an evaluation of concurrent symptoms and contributing factors frequently associated with fatigue, including a mental status examination and laboratory blood tests.[5,19,20] For example, fatigue and depression have been identified as concurrent symptoms in patients with cancer. There are also factors that are causative in the fatigue experience that need to be specifically assessed. These include pain, emotional distress, sleep disturbance, poor sleep hygiene, anaemia, nutrition, activity level, active infection, cardiovascular disease, pulmonary disease, medication side effect profiles, alcohol/substance use, and comorbidities/cancer treatment effects.[5,19,20] These factors require evaluation over time to determine the extent to which they contribute to CRF.[20]

Patients' clinical status (of the underlying cancer) should be determined as a final step in the primary evaluation/diagnostic assessment. Clinical status can be categorised as active cancer treatment, post-treatment with no active treatment except hormonal therapy, or end of life.[5,19] Though some general treatment guidelines apply across all categories, some CRF treatment and management strategies are tailored to a particular clinical status.

3. Interventions/Management

If any treatable contributing factors are identified during the primary evaluation/diagnostic assessment, these should be treated as an initial approach to CRF management and followed by a fatigue re-screening. If no treatable factors are identified, or if treatment of these factors does not yield results, patients should be recommended onto specific interventions based on their clinical status.[5,19,20]

Central to all intervention pathways, stressed in both the NCCN and ESMO guidelines, is family and patient education and counselling. Patients and their families need to be educated on CRF causes and influencing factors; this type of information provision is believed to be effective in the management of fatigue.[2,20] The LC 2018 GPS showed that only 24% of patients with lymphoma who experienced fatigue had a very good understanding of the potential side effects of their

disease and treatment, and only 18% had a very good understanding of side effect management. This is a major gap requiring significant improvement.

There are also general strategies for the management of fatigue. These strategies typically centre on fatigue monitoring and energy conservation.[5,19] Patients with, and survivors of cancer are encouraged to visualise their energy as a bank account; total energy is typically less when you have cancer, so you have to identify the things that draw from this total energy (i.e. stressful relationships, worry, pain, sleep problems) and counter-balance them with positive deposits (exercise, meaningful work, reframing of set-backs, peace-of-mind, healthy eating, time with loved ones).[8,16] There are now apps, for example 'Untire' (www.untire.me), designed to facilitate the identification and tracking of energy withdrawals and deposits.

To keep the total energy bank in the positives, those struggling with CRF may have to make behavioural adjustments relating to planning, prioritising and pacing.[12,17] Patients may need to plan for worse bouts of fatigue during and following treatments, and/or plan-out a structured daily routine where activities are scheduled at times of peak energy. Priorities and realistic expectations must be set; patients can make a list of major commitments and determine order of importance, and then speak to the people involved to manage expectations. Finally, linked to priorities is pacing of activities. Patients must anticipate that things may take a little longer, and must be prepared to delegate tasks, to tend to one activity at a time, and to postpone nonessential activities if necessary.[5,12,16-17]

Following education and the dissemination of general fatigue management strategies, additional interventions may be introduced; in many instances, a combination of approaches must be used.[1,5,19,20]

The main physical interventions recommended include[5,8,19,20]:

- Functional resistance exercise (light weights, strength training)*
- Aerobic or endurance (walking, jogging, swimming, cycling) exercise programs*[13,21-22]
- Nutritional consultation and counselling

These exercise types are recommended for **non-cachectic patients with cancer.*

The main psychosocial interventions recommended include[5,8,19,20]:

- **Psychoeducation**
- **Cognitive behavioural therapy** (CBT)
- **Mindfulness based cognitive therapy** (MBCT)
- **Mindfulness-based stress reduction** (MBSR)
- Mind-body interventions (yoga, reiki)
- Bright white light therapy[10]

The main pharmacologic interventions recommended include[5,8,19,20]:

- Psychostimulants (methylphenidate)[23]
- Antidepressants
- Steroids e.g. short-term use of dexamethasone or methylprednisolone (corticosteroids) in patients with **metastatic cancer***

- Supplements (ginseng, vitamin D)

**Short-term use of dexamethasone or methylprednisolone (in patients with metastatic cancer) is the only pharmacologic intervention recommended by ESMO.*

Providing there is no clear medical explanation for a patient's CRF, studies suggest that exercise and psychological interventions are significantly more effective for improving CRF compared with pharmaceutical interventions overall.[1,8] As such, clinicians should prescribe exercise and psychological interventions, which can be used alone or in combination, as first line therapy for patients experiencing CRF.[1]

HCPs have an important role to play in promoting and supporting the use of evidence-based fatigue management strategies.[24] However, the LC 2018 GPS showed that only 33% of those who experienced fatigue and related issues were referred by their doctor onto further information and support.

4. Re-evaluation

The treatment of fatigue is continuous and as indicated by the re-evaluation phase, leads to a repeating loop of fatigue screening and management. Fatigue may occur or vary in severity at many points throughout the course of a patient's disease and treatment. Re-evaluating the patient's status and making the appropriate modifications are integral parts of comprehensive fatigue management. This includes re-screening and re-evaluating patients after any specific intervention is introduced for CRF.[5,19,20] HCPs should continue to monitor fatigue well beyond treatment completion as CRF has been shown to persist for many years. As was earlier noted, the LC 2018 GPS showed that some patients with lymphoma reported experiencing fatigue for up to 8+ years following treatment.

While there is much similarity between the two clinical practice guidelines, there are some differences. The NCCN CRF guidelines delineate three separate intervention pathways for patients based on if they are in active treatment, post-treatment, or at end-of-life (please visit the NCCN website to view these in detail).

Additionally, ESMO created separate CRF guidelines for elderly patients with cancer (patients ≥65 years old). The approach to screening and scoring CRF is the same as in adult patients with cancer (using 0-10 numeric rating scale, ≥4 indicates moderate to severe fatigue).[20] In the diagnostic assessment phase for those with moderate or severe fatigue, it is very important that a review of all drugs taken by the patient is carried out.[20] In elderly patients, **polypharmacy** increases the risk of drug interaction, and there is also an increased risk of potentially inappropriate medication.[20] Regarding CRF management, the goal of CRF therapy in elderly patients with cancer is maintaining patient's functional independence. Like in adults, if no contributing treatable factors are identified in the diagnostic assessment, the first step is patient and family education. Following this, physical activity and psychosocial interventions are recommended. Pharmacological interventions are not recommended for elderly patients with cancer.[20]

MOVING FORWARD

Fatigue is the leading physical issue affecting the well-being of patients with lymphoma, and it persists long after treatment is completed. The LC 2018 GPS indicated that patients are not being educated about fatigue and fatigue management, and the majority are not being referred onto further information and support for their fatigue.

While efforts have been made towards bettering the understanding, assessment and treatment of CRF, there is still considerable room for improvement in care.

- The mechanistic pathways of CRF need to be better understood and characterised in order to develop interventions that alleviate CRF, as well as to develop lymphoma treatments that do not exacerbate CRF.
- Though current evidence is limited in linking any specific biomarker to the development of CRF, there are promising interventional targets that require consideration and investigation.[14] Maintaining an open and collaborative approach between clinicians and researchers will be key.
- Educational and training programs should be implemented to ensure that HCPs possess the knowledge and skills for proficiency in CRF assessment and management.[5]
- Fatigue should be recognised, evaluated, monitored, documented and treated promptly at all stages of a patient's disease, prior to, during and following treatment.
- Fatigue should be treated as early as possible following diagnosis/at the start of medical treatments to help prevent CRF from becoming chronic in status.[8]
- Implementation of guidelines for fatigue management is best accompanied by interdisciplinary teams who are able to tailor interventions to the needs of the individual patient. Referrals should be made to appropriate specialists and supportive care providers.[5]
- Patients and their families should be informed that fatigue management is an integral part of their total healthcare.
- In order to overcome current barriers, both patients and healthcare providers need to improve their communication about fatigue.

APPENDIX 1.

Possible Biomarkers Involved in the Biological Aetiology of CRF[14]

Biological Process/Mechanism	Possible Biomarkers
Immune response dysregulation	$CD3^+/CD69^+$, $HLA\text{-}DR^+/CD11c^+/CD14$
Impairment of mitochondrial/metabolic function	IGF, C-peptide, adenosine 5'-triphosphate
Inflammation	TNFα, IL6, IL1Ra, TGF, sTNF-RII, C-reactive protein
Associated genes: between impairment of mitochondrial/metabolic function and inflammation	IL-6-174, TNFα-308, PLOD1, NPCDR1, UGT1A1
Dysregulation of HPA Axis	Cortisol, adrenocorticotropic hormone, epinephrine, norepinephrine
Impairment of neuroendocrine function	Testosterone, free and total estradiol, tri-iodothyronine, thyroid-binding and sex hormone-binding globins

APPENDIX 2.

Selected Instruments Used to Measure Cancer-Related Fatigue[6,19]

Unidimensional CRF Measurement Tools

Screening Tool/ Assessment	Number/Type of Dimensions	Type of Scale	No. of Items	Ease of Use	Validated in Patients with Cancer
Brief Fatigue Inventory	1 (severity)	11-point Likert	9	Short, easy to use	Yes, mixed cancers
Profile of Mood States-Fatigue (POMS-F)	1 (severity)	5-point Likert	65 with 7 item fatigue subscale	Long but subscale is reasonable and simple	Yes, mixed cancers
Functional Assessment of Chronic Therapy-Fatigue (FACT-F)	1 (severity)	5-point Likert	13	Easy to use	Yes, mixed cancers
EORTC QLQ-C30*	1 (severity)	4-point Likert	3	Easy to use	Yes, mixed cancers

**EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30.*

Highlight indicates scale met the most quality assessment criteria in Al Maqbali et al 2019[6] review.

Multidimensional CRF Measurement Tools

Screening Tool/ Assessment	Number/Type of Dimensions	Type of Scale	No. of Items	Ease of Use	Validated in Patients with Cancer
Fatigue Symptom Inventory (FSI)	4 (severity, frequency, diurnal variation, interference)	11-point Likert	14	Reasonable	Yes, breast, metastatic, and mixed cancers
Functional Assessment of Cancer Therapy Fatigue (Fact-F)	5 (physical, social/ family, emotional, functional, fatigue)	5-point Likert	41/13	Long but subscale is reasonable and simple	Yes, breast, mixed cancers
Multi-Dimensional Fatigue Inventory (MFI-20)	5 (general, physical, mental, reduced activity, reduced motivation)	5-point Likert	20	Reasonable	Yes, breast, uterine, mixed cancers
Multi-Dimensional Fatigue Symptom Inventory (MFSI-30)	5 (general, physical, mental, emotional, vigour)	5-point Likert	83/30	Variable length, can be complicated	Yes, mixed and breast cancer
Piper Fatigue Score-12	4 (sensory behavioural/ severity, affective meaning, cognitive/ mood)	11-point Likert	12	Easy to use	Yes, breast cancer
Schwartz Cancer Fatigue Scale, Revised	2 (physical and perceptual)	5-point Likert	6	Reasonable and clear	Yes, mixed cancers

Highlight indicates scale met the most quality assessment criteria in Al Maqbali et al 2019[6] review.

GLOSSARY

Aetiology: The cause, set of causes, or manner of causation of a disease or condition.

Autonomic imbalance: The autonomic nervous system is a competing body system. It is called autonomic because it controls things that we do not consciously have to think about, such as blood pressure, heart rate, and other involuntary functions. It is divided into a sympathetic system (fight-or-flight responses) and a parasympathetic system (prepares us for rest, calmness, digestion). Our bodies function best when these two systems are in balance. Prolonged imbalance of the autonomic nervous system in regards to cancer and other disorders usually means the sympathetic function is overactive, and the parasympathetic function is underactive.

Circadian rhythm: A roughly 24 hour cycle in the physiological processes of living beings. They are internally generated, although they can be modulated by external cues such as sunlight and temperature. Circadian rhythms are important in determining sleeping and eating patterns. There are clear patterns of brain wave activity, hormone production, cell regeneration and other biological activities linked to this daily cycle.

Cognitive behavioural therapy (CBT): A structured, time-limited, problem-focused and goal oriented form of psychotherapy. CBT helps people learn to identify, question and change how their thoughts, attitudes and beliefs relate to the emotional and behavioural reactions that cause them difficulty.

Hypothalamic-pituitary-adrenal (HPA) axis: A complex set of direct influences and feedback interactions among three components: the hypothalamus, the pituitary gland, and the adrenal glands. The HPA axis is our central stress response system.

Iatrogenic factors: Effects on a patient resulting from diagnostic and therapeutic procedures undertaken.

Metastatic cancer: Cancer can spread from where it started to another part of the body. The original cancer is called the primary tumour. The cancer in another part of the body is called metastatic, or secondary, tumour. Metastatic cancer has the same type of cancer cells as the primary cancer.

Mindfulness based cognitive therapy (MBCT): An approach to psychotherapy that uses cognitive behavioural therapy methods in collaboration with mindfulness meditative practices and similar psychological strategies. It is an evidence-based group therapy for preventing depressive relapse and treating mood disorders. It reduces depression, anxiety and stress.

Mindfulness-based stress reduction (MBSR): A program that helps you learn to calm your mind and body to help you cope with illness, pain, and stress. MBSR teaches "mindfulness," which is a focus only on things happening in the present moment. Mindfulness is not a time to "zone out" or "space out" but is rather a time to purposefully pay attention and be aware of your surroundings, your emotions, your thoughts, and how your body feels.

Mitochondria (mitochondrial): An organelle within human cells that act as the powerhouses of the cell. Mitochondria take in nutrients, break them down, and create energy rich molecules for the cell. Some cells have several thousand mitochondria while others have none.

Neuronal function: Neurons (also known as neurones, nerve cells and nerve fibres) are electrically excitable cells in the nervous system that function to process and transmit information.

Non-cachectic [patients with cancer]: Patients who do not display cancer cachexia. Cancer cachexia is a wasting syndrome characterised by weight loss, anorexia, asthenia, and anaemia.

Pathophysiology: The study of the changes of normal mechanical, physical, and biochemical functions, either caused by a disease or resulting from an abnormal syndrome.

Polypharmacy: Refers to the concurrent use of a large number of medications, commonly considered

to be the use of five or more. Since polypharmacy is a consequence of having several underlying medical conditions, it is much more common in elderly patients.

Pro-inflammatory cytokines: Cytokines are regulators of the body's responses to infection, immune responses, inflammation, and trauma. Some cytokines act to make disease worse (pro-inflammatory), whereas others serve to reduce inflammation and promote healing (anti-inflammatory).

Psychoeducation: A means of providing education and information to those seeking or receiving mental health services, such as people diagnosed with mental health conditions (or life threatening/ terminal illnesses) and their family members. The information and support provided focuses on bettering understanding and helping patients and their families cope with the illness.

Psychometric properties: Refer to the reliability and validity of a research instrument. Reliability refers to the consistency while validity refers to the test results' accuracy.

Quantitative: relating to, measuring, or measured by the quantity (i.e. number) of something rather than its quality (i.e. description).

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