Brain, Behavior, and Immunity 119 (2024) 507–519

Contents lists available at ScienceDirect

Brain Behavior and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

Review Article

Psychoneuroimmunology in multiple myeloma and autologous hematopoietic stem cell transplant: Opportunities for research among patients and caregivers

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A B S T R A C T

Multiple myeloma (MM) is an incurable cancer and is the leading indication for autologous hematopoietic stem cell transplantation (HSCT). To be eligible for HSCT, a patient must have a caregiver, as caregivers play a central role in HSCT preparation and recovery. MM patients remain on treatment indefinitely, and thus patients and their caregivers face long-term challenges including the intensity of HSCT and perpetual therapy after transplant. Importantly, both patients and their caregivers show heightened depressive and anxiety symptoms, with dyadic correspondence evidenced and caregivers' distress often exceeding that of patients. An extensive psychoneuroimmunology (PNI) literature links distress with health via immune and neuroendocrine dysregulation as well as biological aging. However, data on PNI in the context of multiple myeloma – in patients or caregivers – are remarkably limited. Distress in MM patients has been associated with poorer outcomes including higher inflammation, greater one year post-HSCT hospital readmissions, and worse overall survival. Further, anxiety and depression are linked to biological aging and may contribute to the poor long-term health of both patients and caregivers. Because MM generally affects older adults, individual differences in biological aging may represent an important modifier of MM biology and HSCT treatment outcomes. There are a number of clinical scenarios in which biologically younger people could be prescribed more intensive therapies, with potential for greater benefit, by using a personalized cancer therapy approach based on the quantification of physiologic reserve. Further, despite considerable psychological demands, the effects of distress on health among MM caregivers is largely unexamined. Within this context, the current critical review highlights gaps in knowledge at the intersection of HSCT, inflammation, and biological aging in the context of MM. Research in this area hold promise for opportunities for novel and impactful psychoneuroimmunology (PNI) research to enhance health outcomes, quality of life, and longevity among both MM patients and their caregivers.

1. Introduction

Multiple myeloma (MM) is an incurable cancer of plasma cells and is the leading indication for autologous hematopoietic stem cell transplantation (HSCT). With a median age of 69 years at diagnosis, MM can be associated with a trajectory of frailty including poor physical functioning and fatigue (Rosko et al., 2019). Most MM patients remain on treatment indefinitely, and thus patients and their caregivers face long-term challenges including the intensity of HSCT, ongoing maintenance therapy, and the stress of an inevitable relapse of the disease. Importantly, both patients and their caregivers show heightened depressive and anxiety symptoms (Sherman et al., 2009; Amonoo et al., 2019; Langer et al., 2017; Bishop et al., 2007). Of clinical importance, an extensive psychoneuroimmunology (PNI) literature links stress and

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https://doi.org/10.1016/j.bbi.2024.04.019
Received 16 August 2023; Received in revised form 12 April 2024; Accepted 16 April 2024
Available online 21 April 2024

distress (i.e., depression and anxiety) with health via immune and neuroendocrine dysregulation as well as biological aging. Multiple Myeloma itself hampers immune function, and in patients with elevated distress, immune function may be particularly impaired. Despite the unique implications of PNI pathways in the context of MM for both caregivers and patients, data are remarkably limited in this population.

Depression in MM patients has been associated with poorer outcomes including higher inflammation, greater one year post-HSCT hospital readmissions, (Rosko et al., 2019) and worse overall survival (Tavakoli-Ardakani et al., 2019; El-Jawahri et al., 2017) To be eligible for HSCT, a patient must have a caregiver as caregivers play a central role in HSCT preparation and recovery—and thus it is concerning that caregivers' anxiety and depression sometimes exceed that of patients (Bishop et al., 2007; Fife et al., 2009; Beattie and Lebel, 2011; Langer et al., 2003; Langer, 2003; Langer et al., 2007). Anxiety and depression are linked to biological aging and may contribute to the poor long-term health of both patients and caregivers. Moreover, because MM generally affects older individuals, individual differences in biological aging may represent an important modifier of MM biology and HSCT treatment outcomes. Within this context, understanding the extent to which distress and HSCT accelerate biological aging, separately and together, as well as key biobehavioral pathways (i.e., identification of specific distress constructs and inflammatory mediators) would provide clinically valuable information. As pictured in our conceptual model (Fig. 1), the aim of this critical review[1] is to 1) synthesize the current literature, 2) highlight opportunities for psychoneuroimmunology research, and 3) detail the clinical value/application of psychoneuroimmunology data in the context of multiple myeloma and HSCT caregivers and patients, particularly data on inflammation and biological aging.

2. Multiple myeloma (MM) and its treatment

Multiple myeloma (MM) is a hematologic malignancy of plasma cells. MM occurs as result of neoplastic expansion of plasma cells within the bone marrow and production of a monoclonal immunoglobulin protein, this results in bone destruction, development of anemia, and can result in severe electrolyte disturbances (e.g. hypercalcemia), kidney failure and infectious complications. MM is a disease of aging with a median age at diagnosis of 69 and occurs more frequently in men than in women (1.4:1) (Siegel et al., 2016). MM accounts for 15 % of all hematologic malignancies in the US, (Siegel et al., 2016) and the incidence is expected to double in the next 15 years (Smith et al., 2009). MM incidence is 2 to 3 times higher among African-Americans and the cause of the disproportional incidence is unknown (Waxman et al., 2010). MM is an incurable blood cancer but is highly treatable. The overarching goal of MM directed therapy to use novel therapeutic approaches to induce a deep and durable remission. All patients with MM, will eventually face a relapse of their disease and further systemic therapy is then administered. Patients diagnosed with MM, who are medically fit, are candidates for an Autologous Hematopoietic stem cell transplantation (AHSCT). AHSCT is generally considered the standard of care for newly diagnosed MM patients, with upfront AHSCT associated with a 21-month progression-free survival advantage (Richardson et al., 2022). Autologous indicates that the source of stem cells are derived from the patient. The initial diagnosis and treatment for patients with MM consistent consists of different phases, with variable treatment intensity. Induction therapy, broadly classified as novel systemic treatment, is designed to de-bulk the bone marrow of myeloma cells resulting in myeloma cell death. Induction therapy is personalized to the patient based on patient health, disease biology and end-organ impairment. Generally, MM induction treatment consists of a proteasome inhibitor administered subcutaneously, an immunomodulatory drug (IMiD), dexamethasone, and/or a monoclonal.

antibody administered subcutaneously or intravenously (Callander et al., 2022). Induction treatment for AHSCT transplant is administered until disease control and end-organ optimization lasting approximately 4 months. With disease control, patients then undergo stem cell procurement.

Stem cell collection and procurement is when the patient's stem cell production is boosted using a high dose stem-cell colony growth factor with or without chemotherapy; stem cells are collected from peripheral blood and frozen until HSCT (Giralt et al., 2009). Patients are then admitted to the hospital for high dose chemotherapy (e.g. melphalan) which results in complete ablation of both healthy bone marrow and any residual myeloma cells (myeloablation), followed by re-infusion of the patient's stored stem cell product on hospital day 3. Hospitalization typically lasts 2–3 weeks, during which infection risk is highest as patients await successful HSCT engraftment, involving stem cells recolonization of the bone marrow, the resumption of marrow cell production (hematopoiesis), and reconstitution of the immune system. Tracked daily, engraftment is defined as a sustained neutrophil count $>$ 500 k/μL. Patients remain in the hospital until hematopoiesis is sustained, infections (if developed) are controlled, nausea and vomiting is resolved, electrolytes are stabilized, and the patient is able to tolerate oral intake. Following symptom recovery, patients are able to return home with their caregiver. After $\sim$ 3 months post-HSCT patients begin maintenance therapy (e.g. most often immunomodulatory oral therapy): maintenance therapy is ongoing systemic treatment to maintain disease control, this pill-based therapy is dosed at lower levels and patients obtain monthly blood work to monitor toxicities and efficacy of this therapy over time. Patients with MM receive perpetual therapy, once diagnosed patients receive treatment indefinitely and are followed serially over the patient's lifetime.

In transplant clinical trials, patients who receive standard induction therapy followed by HSCT and maintenance therapy had a 3-year overall survival (OS) of 83.7 % (Stadtmauer et al., 2016), and 6-year OS of 40.9 % (Stadtmauer et al., 2016). Although HSCT has substantially increased overall response rates and durable remissions for the MM population as a whole, (Harousseau et al., 2010; Kumar et al., 2014; Cavo et al., 2010) older MM patients (>65 years of age) have not shared the improvement in survival achieved in younger patients (<65 years of age) (Blimark et al., 2018). Older MM patients are particularly vulnerable to adverse events associated with multi-drug combinations, and treatment discontinuation confers worse outcomes (Palumbo et al., 2012). Furthermore, older patients are more likely to require functional assistance, independent of comorbid conditions (Extermann et al., 1998).

Return to function among patients post-transplant plateaus at one year, leaving many MM patients with only modest improvements in Health-Related Quality of Life (HRQoL), (Cavo et al., 2010) and substantial short and long-term morbidity (DeSantis et al., 2016; Noone et al., 2015). Data on the short and long term physical and psychological health of caregivers are lacking. Nearly half of autologous HSCT recipients develop at least one non-malignant late effect that negatively impacts overall health and functional status; examples include fatigue, neuropathy, and/or sexual dysfunction (Arora et al., 2020). Dynamic functional changes occur among patients with MM and physical function tracks with HRQoL (Rosko et al., 2019; Rosko et al., 2015). Poor mobility, independence of activities of daily living, and frailty are predictive of morbidity and mortality in the myeloma cancer population (Soubeyran et al., 2012). Treatment advances and autologous HSCT

[1] As a critical review, this manuscript aims to evaluate the current body of work and provide a conceptual basis for future scientific inquiry applying psychoneuroimmunology approaches in the context of multiple myeloma. As this is not a systematic review, we do not aim to identify all available literature in this topic area, nor do we provide formal quantitative assessment of prior studies with accompanying methods and results. Rather, as detailed by Grant & Booth (2009), our emphasis is on synthesis and conceptual development. 13. Grant MJ, Booth A: A typology of reviews: an analysis of 14 review types and associated methodologies. Health Info Libr J 26:91–108, 2009.

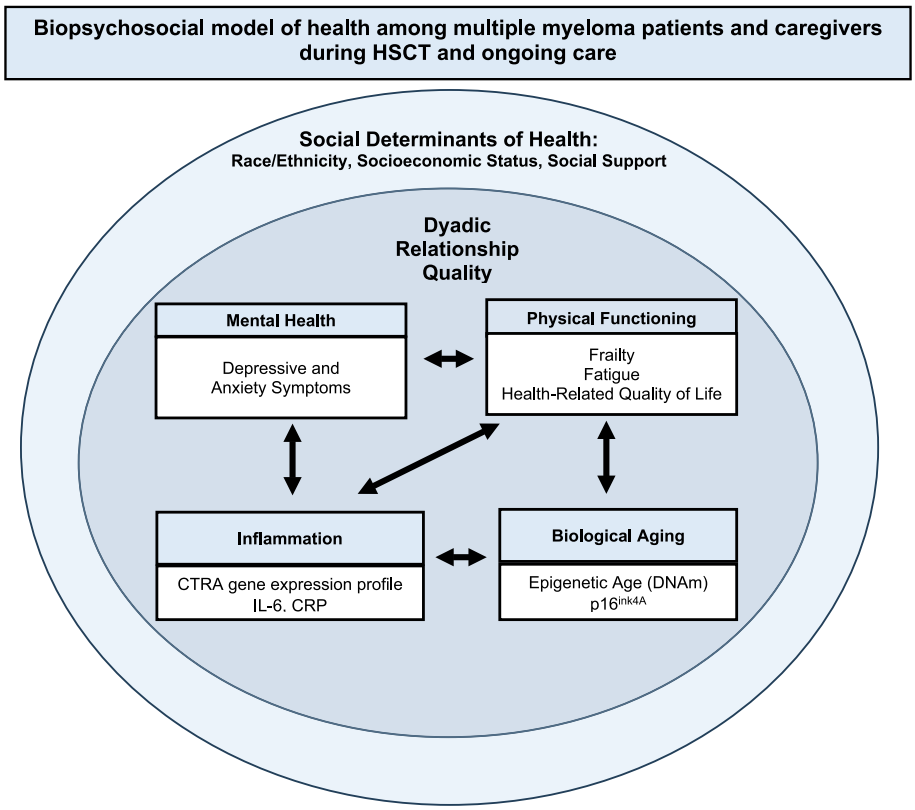

Fig. 1. Key biobehavioral pathways hypothesized to link stress and health among both patients and caregivers in the context of multiple myeloma treatment. Health-related Quality of Life = an individual's assessment of overall physical and mental health, related functional limitations, and life satisfaction. CTRA = conserved transcriptional response to adversity; IL-6 = Interleukin-6; CRP = C-reactive protein; DNAm = DNA methylation; $p16^{INK4A}$ = a protein which functions as a tumor suppressor and cell cycle regulator and is a marker for aging and senescence.

have extended life expectancy in MM; however, the therapy's lasting influence on physical function and psychosocial distress has become more evident as patients live longer.

2.1. HSCT disparities among patients with multiple myeloma

A critical consideration for MM research is adequate representation of individuals impacted by the disease. Moreover, in the context of behavioral health research, careful consideration, and assessment of relevant stressors as well as resilience factors, which may differ based on demographic characteristics, is key. Disparities in HSCT access and survival have been documented for race, ethnicity, socioeconomic status (SES), and age (Al Hadidi, n.d.; Derman et al., 2020; Chamoun et al., 2021; Majhail et al., 2012; Ailawadhi et al., 2018). Among those who receive HSCTs, lower SES has been associated with higher risk for all-cause mortality and non-relapse mortality (Fu et al., 2015). HSCT utilization is more frequent in Whites than African Americans, (Joshua et al., 2010) often contingent on insurance status, (Mitchell et al., 1997) and women are less likely than men to receive an autologous HSCT (Joshua et al., 2010). Population-based Surveillance, Epidemiology and End Results (SEER) studies have reported improved survival of African Americans relative to White populations, (Ailawadhi et al., 2018) despite lower access to therapies such as HSCT. Non-Hispanic Black patients receive MM HSCT at just over one-half the rate (54 %) of non-Hispanic White patients, and fewer non-Hispanic Black or Hispanic patients older than 60 receive MM HSCT compared to White patients (42 % v. 39 % v. 56 %, respectively) (Schriber et al., 2017). Importantly, with equal access to novel therapies and MM HSCT, younger African American patients have superior odds of survival, and older patients (>65) have survival similar to White patients (Fillmore et al., 2019).

One barrier to HSCT access is the lack of a caregiver. Most transplant centers require a caregiver, to assist in post-transplant care (e.g. education, medical appointment management, transportation, medication assistance and management, supportive care for symptoms, household responsibilities). If a patient does not have a friend or family member who is willing or able to provide care, they may be considered ineligible for HSCT, and this problem may be more common for patients with low socioeconomic status. Importantly, for patients who undergo HSCT – there is little to no screening of the caregiver under standard practice. While the presence of a person who can provide instrumental support (e.g., transportation, scheduling, symptom monitoring) is often required, the ability of a caregiver to provide emotional support is not assessed or considered.

Primary caregivers play an instrumental role in the HSCT eligibility, treatment, and recovery process. Yet, MM caregivers themselves may struggle with their own mental, physical, and finance-related issues, which can be triggered or exacerbated by caregiver burden (Meehan et al., 2020; Jamani et al., 2018). Compared to the general population, MM caregivers generally have higher rates of depression and other chronic medical conditions (Jamani et al., 2018). Moreover, those with low socioeconomic status or those in rural areas may be particularly distressed given caregiving's time and financial demands: One rural cancer center found that caregivers of autologous HCST recipients lost an average of $736 when lost wages and out-of-pocket expenses were considered, and they traveled an average of 450 miles in the month post-HSCT. More broadly, when looking across cancer types, approximately one-third of cancer caregivers stopped working and had increased debt (Meehan et al., 2020; Bradley et al., 2023). This financial burden may reverberate to physical and mental health, but such research is limited among MM caregivers – especially in regard to health disparities related to race, ethnicity, sexual orientation, or gender identity. However, the larger cancer literature shows that Hispanic, Black, and LGBTQ cancer

caregivers experience greater caregiving burden and poorer health outcomes, on average, compared to caregivers with non-minoritized identities (Fenton et al., 2022; Tan et al., 2023). Given that patients with MM are even more immunocompromised post-HCST than other (non-transplant) cancer patients, caregiver burden, and therefore caregiver health disparities, may be especially pronounced.

2.2. The prognostic role of inflammation in multiple myeloma

MM is typified by the aberrant propagation of neoplastic plasma cells (Musolino et al., 2017). Proinflammatory cytokines play a central role in MM tumor growth, progression, and spread (Bebnowska et al., 2021). Interleukin (IL)-6 production, a central factor in MM tumor survival and spread, is stimulated by IL-1β in the tumor microenvironment. Thus amplified, IL-6 plays an essential role in the proliferation of myeloma cells, functioning as a crucial growth factor, as does tumor necrosis factor(TNF)-α (Musolino et al., 2017; Mantovani and Garlanda, 2006). High serum IL-6 is associated with a poor prognosis, (Musolino et al., 2017) and pre-transplant elevations in C-reactive protein (CRP; used as an IL-6 surrogate) identify a high-risk subgroup with a poorer prognosis for overall survival (Chakraborty et al., 2018). Proinflammatory factors in circulation can activate nuclear factor kappa B (NF-kB) signaling. The dysregulation of the NF-kB results in further myeloma cell proliferation, survival, and drug-resistance (Roy et al., 2018). Within this context, the role of psychological stress, distress, and sleep disruption in promoting inflammation, along with the potential beneficial effects of emotional support from a caregiver, are highly relevant to disease course. This presents a critical and understudied area of investigation.

2.3. Biological distress pathways

The bone marrow is a complex hematopoietic organ where many different types of hematopoietic stem cells and non-hematopoietic cells reside. The bone marrow microenvironment, or niche, is intricately regulated by mesenchymal stromal cells, perivascular tissue, and endothelial cells, and is surrounded by vascularized and innervated bone (Morrison and Scadden, 2014). The sympathetic nervous system's (SNS) innervation of the bone marrow microenvironment serves as a regulator of hematopoiesis, stem cell trafficking, and engraftment while increasing the rate of hematopoietic stem/progenitor cell departures from the bone marrow (Knight et al., 2020). Both physical and psychological stress activate the SNS, triggering norepinephrine release which stimulates β-adrenergic receptors on normal leukocytes (Black, 2002). The consequent β-adrenergic signaling promotes inflammation, which induces IL-6 production and overproduction of vascular endothelial growth factor (VEGF) (Bierhaus et al., 2003; Thaker et al., 2006; Cole et al., 2010). VEGF production promotes angiogenesis, therefore, this cascade can enhance tumor growth and progression (Hwa et al., 2017). Because β-adrenergic signaling is central to this pathway, patients with hematologic malignancy may be well-matched for beta-blockers to further impede β-adrenergic activation (Hwa et al., 2017). A retrospective epidemiologic study of 1971 patients newly diagnosed with MM illustrated the health relevance of this distress pathway: beta-blocker use was associated with longer overall and disease-specific survival, even after adjusting for key prognostic factors (Hwa et al., 2017).

Propranolol, a non-selective beta-blocker, was used in patients with MM in a phase 2 randomized controlled biomarker trial (Knight et al., 2020). The drug or placebo was dispensed one week prior to, and four weeks post-HSCT, a period of heightened psychological and physiological stress, as well as heightened inflammation (Sherman et al., 2009; Wang et al., 2014). Propranolol inhibited key molecular risk-related pathways including the Conserved Transcriptional Response to Adversity (CTRA) gene expression profile. The CTRA is β-adrenergically mediated and characterized by increased inflammatory gene expression as well as decreased expression of genes involved in type I interferon antiviral responses and antibody synthesis in peripheral blood mononuclear cells.

Decreases in CTRA gene expression and $CD16^{-}$ classical monocyte activation were greater among propranolol-treated patients compared to controls, with the former also showing greater up-regulation of gene transcripts associated with $CD34^{+}$ cells and down-regulation of gene transcripts associated with $CD33^{+}$ myeloid progenitors (Springer Nature, 2022). CD34 + cells are marker of hematopoietic stem cell progenitors required for hematopoietic engraftment and reduced CD33 suggests a reduction in the myeloid lineage (more applicable to an allogenic HSCT). Subsequent analyses showed nonsignificant trends toward faster engraftment and fewer post-transplant infections in propranolol-treated patients (Knight et al., 2020). The role of propranolol as adjuvant therapy to augment post-transplant outcomes is of relevance to the MM population, particularly for engraftment, post-transplant infections and progression free survival.

Separate cross-sectional natural history studies have linked elevated CTRA to both lower patient SES and elevated risk of relapse following allogeneic hematopoietic cell transplantation for leukemia (Knight et al., 2019). These CTRA analyses demonstrate how psychological distress can alter neuro-immune interactions in ways that complicate the quality or speed of post-transplant immune reconstitution, (Knight et al., 2013) a noteworthy concern in light of depression and anxiety among patients with MM, described below.

3. Depression, anxiety, and inflammation in patients and their caregivers

As detailed below, PNI pathways are relevant to health among patients as well as their caregivers. While we propose that the key pathways linking distress, biology, and physical health and essentially the same among patients and caregivers, there are clearly unique considerations for patients in terms of both the impact of MM on stress biology and the implications of stress-induced immune dysregulation for disease progression.

3.1. Relevance of PNI models among patients

Given the role of inflammation in MM disease progression, explicating psychoneuroimmunology pathways linking psychological factors with immune function in MM patients is of importance. Depression and anxiety are prevalent among HSCT patients in the interval between the pre-transplant evaluation and one-year post-transplant follow-up (Braamse et al., 2016). Clinically meaningful levels of depression were reported at stem cell collection in 40.4 % of patients with MM, rising to 48.4 % post-transplant (Sherman et al., 2009). A longitudinal study of HSCT recipients showed that 44 % met clinical criteria for depression, anxiety, or posttraumatic stress disorder within 100 days post-transplant (Lee et al., 2005). Psychological recovery trails behind physical recovery, and a third of HSCT recipients reported clinically significant depressive symptoms 90 days post-transplant; 79 % reported continued general psychological distress one year post-transplant (Syrjala et al., 2004). Emotional distress remains problematic in 20 % to 45 % of long-term HSCT survivors, and clinical depression may be present in 9 % to 20 % (Syrjala et al., 2012).

Depression in HSCT patients predicts adverse consequences across multiple domains. For example, higher pretreatment depression predicted slower white blood cell (WBC) and neutrophil recovery after HSCT, as well as higher inflammation (Tavakoli-Ardakani et al., 2019; McGregor et al., 2013). This is concerning because longer periods of leukopenia and neutropenia increase risk for infectious complications, (McGregor et al., 2013; Knight et al., 2014) and inflammation promotes MM cell growth (Wang et al., 2015). Depression in HSCT patients has also been associated with a greater risk for rehospitalization, fewer days out of the hospital during the first 100 days post-HSCT, and greater one year mortality following HSCT (Rosko et al., 2019; El-Jawahri et al.,

2017; Richardson et al., 2018).

In Rosko's prospective cohort study of 100 patients, (Rosko et al., 2019) one-third of the patients reported clinically borderline or definite levels of anxiety both before and after HSCT using the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983). Nearly one-fifth of the patients screened positive for depressive symptoms prior to HSCT, and 11 % post-HSCT. After HSCT, most patients lost weight and showed deficits in Karnofsky Performance Status (KPS). Patients with distress and physical frailty were more likely to be re-admitted to the hospital, particularly for those with higher anxiety and depression. Consistent with other studies, (Sherman et al., 2009; Braamse et al., 2016; Lee et al., 2005; Syrjala et al., 2004) anxiety and depression were prevalent both before and after HSCT and were significantly associated with hospital readmission. However, neuroendocrine and immune factors which may mediate the association between distress and health outcomes remain largely unexamined.

An additional key factor in the PNI literature, sleep disruption poses notable problems for HSCT recipients; over 50 % report difficulties pre-transplant, ~82 % experience moderate to severe sleep disturbances during transplant hospitalization, and 20–43 % have continuing problems post-transplant (Amonoo et al., 2019; Jim et al., 2014). Sleep problems increase depression risk two-fold (Irwin, 2015). Sleep loss stimulates inflammation, thus facilitating depression (Irwin, 2019; Irwin et al., 2013). In turn, heightened inflammation disrupts sleep (Lopresti et al., 2013; Raison et al., 2010).

Unique to MM is the associated bone destruction, which results in bone pain for 60 % of patients presenting with skeletal bone disease at diagnosis (Kyle et al., 2003). Pain, a notable stressor, generates inflammatory responses, (Griffis et al., 2013; Zhou et al., 1993) and amplified pain sensitivity serves as an additional inflammatory source that, in turn, provokes depressive symptoms (Benson et al., 2012; Watkins and Maier, 2005). Greater pain is associated with a higher prevalence of depression, and improvements in depression are correlated with declines in pain (Fishbain et al., 2014). Pain worsens subthreshold depressive symptoms, thereby increasing the risk for depression recurrence (Gerrits et al., 2014). Understanding the bi-directional and mediating pathways linking pain, inflammation, and distress in the context of MM would allow for new intervention approaches.

Given the co-occurrence and bi-directional nature of distress, pain, and sleep disturbance, addressing one factor is likely to have beneficial downstream effects on others. Indeed, together sleep and pain serve as additional, independent accelerators for depression and inflammation in patients with MM. These factors act in tandem, building on each other. Disturbed sleep exacerbates pain and fatigue (Irwin et al., 2012). Conversely, pain clearly impairs sleep (Irwin et al., 2012). This has likely physiologic consequences as sleep problems and chronic pain are associated with accelerated Horvath epigenetic age, (Cruz-Almeida et al., 2019; Carroll et al., 2017) a measure of DNA methylation associated with all-cause mortality (Horvath, 2013).

Furthermore, heightened inflammation induces or intensifies "sickness behaviors" including negative mood, fatigue, anhedonia, increased pain sensitivity, loss of appetite, and cognitive deficits, (Dantzer et al., 2008; Raison et al., 2006; DellaGioia and Hannestad, 2010) a bidirectional pathway through which inflammation also fuels depression (Kiecolt-Glaser et al., 2015). In accord with these data, heightened inflammation, particularly IL-6, was associated with greater depression, pain, disturbed sleep, fatigue, and lack of appetite among patients with MM during transplantation (Wang et al., 2015).

Given the incurable nature of MM, the threat of relapse and concerns about longer-term survival can continue to fuel depression and anxiety as physical symptoms decrease (Fife and Fausel, 2010). Higher depressive symptoms following HSCT predict poorer adherence with key health behaviors in accordance with provider recommendations (oral hygiene, exercise programs, nutrition, and prescribed medications), consistent with the extensive literature that has shown depression's reliable association with nonadherence across multiple diseases and disorders (Mumby et al., 2012; Bishop, 2009).

3.2. Relevance of PNI models among caregivers

As reviewed, PNI models have unique implications for MM patients given the immune and inflammatory pathways directly affecting the disease. An additional, typically overlooked population is MM caregivers. Patients with MM must have a caregiver to be eligible for HSCT at most transplant centers. Despite a demanding and essential role in patient care, caregivers receive limited to no support in terms of caregiver training or mental health assessment or care. As detailed below, distress and social isolation are common experiences among MM caregivers, which, in turn, presents risks to their mental and physical health.

Caregivers play a central role in the *peri*-transplant period and in the patient's recovery. After discharge, the patient's immune recovery requires a period of pathogen protection followed by coordinated complex care for months to years with hematologist/oncologists, sub-specialists and allied health professional services (e.g. physical therapy, etc). The caregiver's schedule includes responsibility for medical care tasks (medication assistance and frequent outpatient visits), coordinating of medical visits (transportation, scheduling), maintaining cleanliness, temperature monitoring, symptom management, and food preparation safety to avoid atypical infections, among other challenges. Caregiver support can influence the patient's psychological and physical recovery, (Fife and Fausel, 2010) and inquiries about caregiver adjustment are part of the recommended screening practice guidelines for long-term HSCT survivors (Majhail et al., 2012). For most MM HSCT patients, the primary caregiver is a spouse or romantic partner (referred to as "partner" herein) (Fife et al., 2009; Rini et al., 2011; Eldredge et al., 2006). The primary caregiver in allogeneic HSCT tends to be the spouse/partner most commonly (~65 %) followed by the parent (12 %) or other (18 %) (Laudenslager et al., 2019). The primary caregiver for patients with multiple myeloma is similar and is described as the spouse/partner 68 % of the time (O'Donnell et al., 2022). In addition to the general issues that affect many caregivers, spousal caregiving is additionally complicated by risk for social isolation; for example, one study of spousal caregivers in the context of dementia found that, over a five year follow-up, caregivers lost approximately 1/3 of their social support network (Clay et al., 2008). Although many HSCT studies have focused on the benefits of social support from multiple people, most transplant recipients name their partner as their primary caregiver. Accordingly, the intimate relationships of HSCT recipients/partners deserve particular focus (Rini et al., 2011).

Treatment-related tasks restrict caregivers' social roles and activities, often leaving them more reliant on their partner. In the context of spousal caregiving, the spousal relationship usually becomes the central source of support for both individuals (Rini et al., 2011). Effective partner support matches the patient's needs for emotional, instrumental, and informational support in amount and type; when a caregiver partner provides problematic support, it has a negative impact (Rini et al., 2011). For example, men and women who were 1–3 years post-HSCT were substantially less distressed when their partner's support was effective, in contrast to ineffective, and the quantity of partner support did not predict the patient's distress (Rini et al., 2011).

Given the partner's central role, it is concerning that caregivers' anxiety and depression may exceed that of the patient, (Bishop et al., 2007; Fife et al., 2009; Beattie and Lebel, 2011; Langer et al., 2003; Langer, 2003; Langer et al., 2007) particularly among women (Langer et al., 2017; Bishop et al., 2007; Langer et al., 2003). Women are more likely to be HSCT caregivers than men, and female spousal MM caregivers report greater distress than their male counterparts (Kim et al., 2017). A husband's illness may influence the wife's depressive symptoms more than the reverse (Min et al., 2019).

It is well-established that depressive symptoms and general distress are affected by marital/relational contagion (Kiecolt-Glaser and Wilson,

2017). Specifically, when one partner exhibits greater depressive symptoms, this often corresponds with higher levels of depression in the other partner (Kiecolt-Glaser and Wilson, 2017). Moreover, such effects are seen in longitudinal studies, with increased in depressive symptoms over time in one partner predicting increases in the other partner's symptoms (Pruchno et al., 2009; Monin et al., 2016). Emotions that are negative or characterized by high-arousal show particular dyadic correspondence (Schoebi, 2008; Saxbe and Repetti, 2010). When couples are managing daily life stressors together, negative emotions are intensified, enhancing risk of transmission when both partners are affected, as is the case for MM (Berg et al., 2011).

The effects of marital/relational contagion on distress have direct implications for physical functioning among both caregivers and controls. Symptoms of depression and the ability to engage in activities of daily living reciprocally influence each other among older adults. That is, functional limitations heighten the risk of depressive symptoms, while depressive symptoms enhance the risk of functional limitations (Hoppmann et al., 2011). As one example, older adults experiencing frailty also experience elevated risk for disability, falls, hospitalization, depression, and early mortality (Monin et al., 2016). Moreover, when examined longitudinally, depression was predictive of later frailty, while frailty, in turn, presaged subsequent depression (Monin et al., 2016). In terms of dyadic correspondence, among couples, frailty in one partner was predictive of frailty in the other partner (Monin et al., 2016). In addition, greater depression in one partner predicted greater depression in the other (Monin et al., 2016). Inflammatory mechanisms underly both depression and frailty, and chronic inflammation is one key biological pathway that may fuel declines in physical function that lead to frailty, disability, accelerated biological aging and, ultimately, death (Ershler and Keller, 2000).

Highlighting the increased risk of frailty among caregivers as compared to their non-caregiving peers., studies with community adults show that older caregivers have a greater chance of becoming frail, (Potier et al., 2018) and pre-frailty in community caregivers approaches 60 % (Maximo et al., 2020). Inflammatory pathways are mechanistically implicated in the link between caregiving and frailty risk. Work from Steve Cole and colleagues (Kim et al., 2021) demonstrated linkages between proinflammatory gene expression and caregiving stress, loneliness, and lack of social support among caregivers during the first year after a patient's colorectal cancer diagnosis. Specifically, this effect was found in relation to the Conserved Transcriptional Response to Adversity (CTRA) pattern of gene expression, characterized by up-regulation of inflammatory pathways, and down-regulation of viral monitoring. These data showed that these negative caregiving-related effects were most pronounced when caregivers experienced low social support and loneliness, and demonstrate the biologic impact of distress on caregivers following a cancer diagnosis (Kim et al., 2021). Neither the frailty trajectory nor changes in CTRA gene expression among spousal HSCT caregivers has been characterized, representing important directions for future investigation.

3.3. 3.3.The importance of relationship quality for both patients and caregivers

As reviewed, both patients and caregivers are each at elevated risk for anxiety, depression, and related inflammatory sequelae in the context of MM treatment and caregiving. Moreover, the risks for depression are contagious: having a depressed partner doubles the likelihood of being diagnosed with depression (Kiecolt-Glaser and Wilson, 2017; Hippisley-Cox et al., 2002). In addition, given the central role of the caregiving relationship, relationship quality is a crucial factor for determining well-being. Even though older couples' relationships are typically closer (i.e., characterized by greater intertwinement of daily routines and activities) than those of younger adults, (Kiecolt-Glaser and Wilson, 2017) relationship satisfaction is far from universal, and the high demands of HSCT can strain relationships (Langer et al., 2017; Akgul and Ozdemir, 2014; Langer et al., 2010; Fife et al., 2013). In one example from an allogeneic stem cell transplant sample, spouses' marital adjustment scores were comparable to each other pre-transplant (9 % scoring in the dissatisfied range); however, by 6 months post-transplant, 24 % of female partners scored in the dissatisfied range, and women's dissatisfaction persisted for two years, while male partners' scores did not change (Langer et al., 2003). In another study, partners reported lower relationship satisfaction and higher negative affect than patients over the first year post-HSCT (Fife et al., 2013). An extensive review of recent relationship research concluded that those couples who were less satisfied prior to stressful life transitions were more likely to report subsequent declines in relationship satisfaction (Karney and Bradbury, 2020).

Relationship distress heightens depressive symptoms and increases the risk for syndromal depression (Beach et al., 2014). The association is bidirectional: discord with the partner leads to increased depressive symptoms over time, (Wilson and Marini, 2023) and depression degrades relationship quality (Beach et al., 2014). Individuals with depression report more stressors, both major and minor, than people who are not depressed, and depression also heightens emotional responsivity to stressors (Hammen, 1991; Husky et al., 2009; O'Grady et al., 2010).

Relationship dissatisfaction, a potent chronic stressor, elevates health risks (Kiecolt-Glaser and Wilson, 2017; Kiecolt-Glaser and Newton, 2001; Robles, 2014). A series of well-controlled studies of heterosexual couples from Kiecolt-Glaser's lab have provided important mechanistic data; frequent negative or hostile behavior during relationship conflict, a signature of relationship distress, (Kiecolt-Glaser and Newton, 2001; Kiecolt-Glaser, 2018) substantially augmented adverse endocrine and immune changes, (Kiecolt-Glaser and Newton, 2001; Kiecolt-Glaser et al., 1997; Kiecolt-Glaser et al., 1998; Kiecolt-Glaser et al., 2005; Kiecolt-Glaser et al., 1993; Kiecolt-Glaser et al., 1996; Kiecolt-Glaser et al., 2015; Kiecolt-Glaser et al., 2003) including enhanced proinflammatory cytokine production (Kiecolt-Glaser et al., 2005; Kiecolt-Glaser et al., 2015). Other researchers have also shown that lower partner support and greater partner strain are associated with higher levels of inflammation, with stronger effects among older adults compared to younger adults (Whisman and Sbarra, 2012; Donoho et al., 2013; Wilson et al., 2021; Madison et al., 2023). In addition, chronic interpersonal stressors, including cancer caregiving-related distress, promote the expression of CTRA genes associated with proinflammatory signaling (Kim et al., 2021; Miller et al., 2009). Indeed, relationship discord's notable consequences include an amplified risk for inflammation-related disorders in addition to depression. These include cardiovascular disease, metabolic syndrome, diabetes, and poor wound healing (Beach et al., 2014; Kiecolt-Glaser et al., 2005; Whisman et al., 2014; Gallo et al., 2003; Gallo et al., 2003; Troxel et al., 2005; Joseph et al., 2014; Orth-Gomer et al., 2000).

4. Future directions: Assessment of molecular and functional aging

As reviewed, psychoneuroimmunology models have great potential for advancing understanding of mental and physical health among patients and caregivers in the context of MM. However, very little work has been conducted in this area. With the goal of stimulating research in this area, herein we aim to highlight particularly promising opportunities of investigation featuring molecular aging biomarkers and functional capacity assessment, and we delineate the potential clinical impact of this research direction. Senescent cell accumulation and genome-wide changes in DNA methylation are two critical elements of molecular aging. Senescent cells are viable but cannot proliferate due to persistent metabolic, oncogenic, genotoxic, or environmental stress. Therefore, the accumulation of senescent cells limits physiologic resiliency. DNA methylation is a direct modification of the genome, which can be inherited through cell division and influence gene expression.

Understanding how DNA methylation patterns change across the genome with age has led to the development of epigenetic clocks, algorithms that estimate biological age based on the methylation state of key DNA methylation sites. Importantly, both cellular senescence and epigenetic alterations directly correlate with psychological distress and inflammation.

Representing a direction of high clinical relevance, we and others have published the effects of MM HSCT on biologic aging, yet effects of HSCT-related psychosocial stress and the contribution of caregiver physical, mental and relationship health is yet to be determined. Two key indicators of biological aging – $p16^{INK4a}$ (p16), a marker of cellular senescence, and epigenetic age, a series of DNA methylation-based biological clocks – are linked with heightened morbidity and mortality (Marioni et al., 2015; Breitling et al., 2016; Hannum et al., 2013; Teyssier et al., 2012; Marioni et al., 2015; Marioni et al., 2019). Both have associations with inflammation, and both are linked to depression and anxiety (Teyssier et al., 2012; Liu et al., 2009; Beach et al., 2015; Xiao et al., 2021; Han et al., 2018; Han et al., 2021; Protsenko et al., 2021). In addition, these two biomarkers can change within a relatively short timeframe (e.g., two years or less) (Liu et al., 2009; Boks et al., 2015). Epigenetic age and p16 have been associated with an increased risk for cancer and greater cancer-related mortality (Shen et al., 2020; Muss et al., 2020; Horvath and Raj, 2018; Guida et al., 2019). Although both biomarkers reflect aging and predict frailty, (Rosko et al., 2019; Breitling et al., 2016; Shachar et al., 2020; Smitherman et al., 2020) they assess different age-related molecular changes: p16 and epigenetic age are not significantly correlated, but both are independently associated with chronological age. (Burd et al., 2020) Thus, these markers provide novel, nonredundant aging metrics.

4.1. Cellular senescence: p16

The expression of p16 in human peripheral blood T lymphocytes (PBTL) increases exponentially with chronological age, rising nearly 10-fold over 60 years (Liu et al., 2009). Functionally, p16 prevents cells from replicating, thereby limiting the regenerative capacity of tissues. Evidence from animal models suggests that age-related increases in p16 play a causal role in age-related disease. Synthetic deletion of p16-expressing cells in old mice attenuates multiple age-related pathologies and decreases the side effects of genotoxic chemotherapies (Martin et al., 2014; Demaria et al., 2017; Acklin et al., 2020). In humans, p16 expression is associated with markers of poor physical function, frailty, and physiologic aging, including poorer mobility, lower muscle strength, and greater central obesity, as well as elevated IL-6 (Liu et al., 2009; Guida et al., 2019). The combined induction of p16 during chronologic aging, and its causal links to age-related physiologic declines make it an excellent aging biomarker (Martin et al., 2014).

Nevertheless, chronological age explains only 40–42 % of the variance in p16 expression (Teyssier et al., 2012; Liu et al., 2009). Additional factors that contribute to the variance in p16 expression include psychological factors and health behaviors. For example, among patients with major depressive disorder, p16 levels were almost double that of matched controls, and higher anxiety scores were strongly correlated with greater p16 expression in the group with depression (Teyssier et al., 2012). Similar associations have been reported in community samples between greater psychological stress and higher p16 mRNA (Rentscher et al., 2019). Furthermore, diet, exercise, and sleep have reliable relationships with depression as well as healthy aging, and they are also associated with p16 (Liu et al., 2009; Schafer et al., 2016; Carroll et al., 2016; Carroll and Prather, 2021; Alvaro et al., 2013).

Recent evidence supports p16′s potential prognostic utility. For example, higher PBTL p16 expression was a risk factor for breast cancer, p16 was higher in more aggressive tumors than those that were less aggressive, (Shen et al., 2020) and p16 predicted toxicity in chemotherapy-treated patients with breast cancer (Muss et al., 2020). In addition, Black patients with breast cancer and controls had higher p16 than their White counterparts (Shen et al., 2020; Zannas et al., 2015).

Chemotherapy can induce cellular senescence in normal tissues. In turn, these senescent cells can boost both local and systemic inflammation, exacerbating the side effects of chemotherapy (Demaria et al., 2017). However, data from patients with breast cancer showed that the accumulation of senescent cells *prior to treatment* also predicted post-treatment fatigue (Demaria et al., 2017). Pretreatment PBTL p16 expression was ~ 40 % greater among women who subsequently reported post-treatment fatigue than those who did not (Demaria et al., 2017). These age-adjusted data suggest that the accumulation of senescent cells prior to chemotherapy predicts subsequent risk for fatigue (Demaria et al., 2017). In fact, compared to women in the lowest quartile of p16 expression, those in the highest quartile had a ~ 9-fold increase in the relative risk of severe fatigue (Demaria et al., 2017). Representing a key opportunity for future investigation, prospective research designs would provide a way to address this issue in patients undergoing HSCT.

Remarkably, data from Rosko, Burd, and colleagues, demonstrated that increased PBTL p16 expression following HSCT was equivalent to 33.7 years of chronological aging (Rosko et al., 2015). Confirming these findings, another group subsequently showed that p16 increased 3.05-fold post-HSCT among patients undergoing an autologous HSCT, or ~ 30 years of chronological age (Wood et al., 2016). Importantly, there is notable variation in these data, with some patients showing little change, while a third of the sample had values equivalent to 44 years of aging or greater. This variability is of great interest. What patient and partner characteristics predict the extent of accelerated biological aging and if these molecular changes predict HSCT treatment response, frailty, and functioning is still unknown.

4.2. DNA methylation and epigenetic age

Epigenetic changes in DNA methylation (DNAm) can alter gene expression, (Needham et al., 2015) and DNA methylation patterns change with advancing age. In an effort to use these changes to predict longevity and health-related outcomes, multiple epigenetic clock algorithms have been developed. These DNAm age metrics use dimensional reduction strategies to identify patterns among hundreds of methylation sites throughout the genome associated with chronological age (e.g., Horvath and Hannum, considered first-generation clocks) and, more recently, distinct aging phenotypes, including mortality (e.g., PhenoAge, GrimAge—second generation clocks). A prominent third-generation model DunedinPACE (Dunedin (P)ace of (A)ging (C)alculated from the (E)pigenome) indexes the *pace* of aging, (Belsky et al., 2022) trained on longitudinal trajectories of physiological changes in a single-year birth cohort rather than a cross-sectional sample like the other clocks. Many studies have found that the clocks share small to moderate correlations with each other, leading some researchers to conclude that the clocks may index different aspects of the aging process (Belsky et al., 2018; Fransquet et al., 2019; Oblak et al., 2021). In a *meta*-analysis of 156 studies where quantitative comparisons were possible for four of the clocks (Hannum, Horvath, PhenoAge, and GrimAge), all four predicted mortality rates most strongly, with varying degrees of magnitude, and also predicted the onset of chronic diseases such as cancer and cardiovascular disease (Oblak et al., 2021). Although many outcomes were not available in sufficient numbers for quantitative *meta*-regression, individual studies have also linked DunedinPACE, PhenoAge, and GrimAge to an advanced aging phenotype, such as poorer lung function and physical function (balance, walking speed, grip strength, functional limitations) as well as worse cognitive performance (Belsky et al., 2022; Faul et al., 2023). A higher DNAm age is associated with greater activation of proinflammatory and interferon pathways, and lower activation of transcriptional/translational mechanisms, and DNA damage responses, providing mechanistic links (Levine et al., 2018).

Beyond established correlations between DNAm aging and cancer

incidence, not surprisingly, cancer treatment has been implicated in age acceleration. Indeed, radiation and chemotherapy led to acute epigenetic age acceleration and an increase in the number of senescent T-lymphocytes in the blood of patients with breast cancer (Sehl et al., 2020). In a study of breast cancer survivors ages 60 and older, (Rentscher et al., 2023) those who underwent chemotherapy were ~ 2 years older on epigenetic clocks compared to matched controls even up to 5 years after study enrollment, post-surgery and before systemic therapy. Ultimately, examination of multiple clocks within the context of MM and HSCT is needed to address gaps in the literature, as prediction algorithms are typically built from cancer-free datasets.

A fast-growing body of literature also links key psychosocial factors to DNAm aging. In particular, Crimmins argued that the social determinants of health should shape the aging process, and thus coined the term *social hallmarks of aging*, which include: adverse life events, adverse psychological states, adverse behaviors, low socioeconomic status, and minority status (Crimmins, 2020). Indeed, all of these have been associated with DNAm aging. For example, individuals who experienced childhood adversity showed at least two years of epigenetic age acceleration over the course of 10 years, from adolescence to young adulthood, compared to those who had no history of childhood adversity (Copeland et al., 2022). Likewise, cumulative lifetime stress in African Americans predicted accelerated epigenetic aging (Zannas et al., 2015). A common companion to stress, depression has been linked to higher DNAm age, (Han et al., 2018; Han et al., 2021; Protsenko et al., 2021; Oblak et al., 2021) including a significant *meta*-analytic correlation with GrimAge (Oblak et al., 2021). This association is consistent with a dose–response model in which increased symptom severity predicts greater DNAm aging (Han et al., 2018; Han et al., 2021; Protsenko et al., 2021). Moreover, prior work has documented that these risk factors can compound: depression accentuated the age-accelerating effect of childhood adversity (Han et al., 2018). In terms of adverse health behaviors, the aforementioned *meta*-analysis documented strong age-accelerated associations of alcohol use with GrimAge as well as Horvath and Hannum clocks (Oblak et al., 2021). In the same *meta*-analysis, smoking and physical activity shared reliable correlations with GrimAge and PhenoAge in the expected directions (Oblak et al., 2021). In further confirmatory evidence of the social gradient, the *meta*-analysis showed significant links between lower education and accelerated GrimAge, PhenoAge, and Hannum measures (Oblak et al., 2021). Finally, racial minority status also may contribute to accelerated aging. For instance, Black breast cancer survivors' aging accelerated more quickly over time compared to non-Hispanic White survivors, according to Horvath and PhenoAge measures (Rentscher et al., 2023). Likewise, among participants in the Women's Health Initiative study, Black postmenopausal women had higher DNAm ages than White women, and this partially explained their higher rates of mortality (Liu et al., 2019). In parallel, racial discrimination predicts accelerated aging, (Brody et al., 2016) which may contribute to these race-based disparities.

Complementing the literature that connects DNAm aging to psychosocial risk factors, Epel posited that psychosocial resilience may have a rejuvenescent effect on the aging process by bolstering reserve capacity (Epel, 2020). For example, older adults with higher-quality friendships and more contact with friends and children had a slower pace of aging (measured using DunedinPACE) and younger GrimAge (Hillmann et al., 2023). Moreover, psychosocial resilience may offset the accelerating effects of the social hallmarks of aging. In support of this hypothesis, a study that harmonized longitudinal cohort data from three countries documented that upward social mobility—moving from a lower socioeconomic class in childhood to a higher level in adulthood—was associated with younger DNAm ages compared to those with consistently low SES across the lifespan (Fiorito et al., 2017). In parallel, among two cohorts of African American youth, those who had supportive family environments were protected from the age-accelerating effects of racial discrimination (Brody et al., 2016). Further, in a sample of paramedics in training, high levels of social support offset the link between job-related psychological distress and accelerated GrimAge (Mehta et al., 2022). Likewise, in a community sample, the use of healthy emotion regulation strategies buffered the age-accelerating effects of cumulative stress on GrimAge (Harvanek et al., 2021). Taken together, many sources of psychosocial resilience show promise for counteracting the age-accelerating influences of social determinants.

4.3. Characterizing frailty in hematologic malignancy

One of the greatest challenges in caring for older adults with hematologic malignancy is the need to individualize therapy; balancing HSCT efficacy with toxicity. Aging is heterogeneous, and candidacy for HSCT cannot be measured by chronologic age alone. Currently, clinicians are left to estimate the risk for HSCT toxicity based on clinical factors such as age, comorbidities, and performance status, but these metrics alone do not reliably predict life expectancy, functional capacity, or risk of treatment complications (Wedding et al., 2007; Hurria, 2012). After treatment, physical functioning in some older cancer survivors returns to relatively normal levels, while others experience continuing impairments or follow a downward course. HSCT has been described as psychosocial transition and understanding the influence of physical impairment, psychosocial distress, and sociodemographic factors with aging is complex (Wall et al., 2023; Parkes, 1967). Thus, transdisciplinary, longitudinal assessments of psychological, biological, and functional status would move the field forward by providing valuable longitudinal data addressing the key factors underlying this heterogeneity (He and Sharpless, 2017).

Such evaluations should include fall history, social support, cognitive and psychologic status, sensory loss, nutritional status, and comorbidities. These represent occult factors, unique to aging, that contribute to adverse events in MM treatment. A Geriatric Assessment (GA) is a comprehensive evaluation of overall health including functional abilities, distress, cognitive function and social support system aimed to identify and intervene upon age-related vulnerabilities. The assessment includes a range of domains including physical performance, nutritional status, polypharmacy, psychosocial assessment, cognitive screening, and identification of geriatric syndromes to characterize overall health or to identify frailty. A Geriatric Assessment is an established method to assess toxicity, morbidity, and mortality risks in cancer populations independent of performance status and age, (Pal et al., 2010; Rodin and Mohile, 2007; Hamaker et al., 2014) but remain understudied in MM. Critically, adults ages 65 and older with MM have high rates of early mortality, and among the *lowest* reported physical and mental health-related quality of life scores among cancer populations (Kent et al., 2015; Krok-Schoen et al., 2018).

Critical to this work is that accelerated aging, as measured through frailty indices, has been shown to be associated with important clinical outcomes, such as treatment side effects/effects, decisions to use lower intensity chemotherapies, progression-free survival, and overall survival. The International Myeloma Working Group (IMWG) frailty calculator is a commonly used index to measure the impact of frailty on MM patient outcomes (Palumbo et al., 2015). Many investigators have demonstrated the value of the IMWG frailty score in predicting overall survival, drug-discontinuation, and progression free survival (Engelhardt et al., 2016; Murillo et al., 2019; Belotti et al., 2020; Yao et al., 2022). Examples of myeloma therapeutic decisions guided by frailty indices have shown that intermediately frail patients can be spared of dexamethasone in maintenance therapy, (Larocca et al., 2021) trials are also examining how inductions strategies can be intensified for fit patients and attenuated for frail patients, (Coulson et al., 2022) or alternatively clinical trials are designed for patients with multiple myeloma based on robust measures of frailty (Mateos et al., 2023; Groen et al., 2023). Frailty is not simply a concern of functional status, but has major therapeutic consequences and downstream clinical implications for patients with multiple myeloma.

5. Future directions in Psychoneuroimmunology, multiple Myeloma, and autologous hematopoietic stem cell transplantation

Aging is inevitable, but biological aging trajectories vary substantially across individuals and can be modified through behavioral interventions (Schafer et al., 2016; Fitzgerald et al., 2023). There are currently important gaps in knowledge with respect to the ability to identify patients with MM and caregivers at risk for an accelerated aging phenotype, as well as those who are more resilient (Guida et al., 2019). Clearer identification of both the risk-related and protective dimensions would provide a strong foundation for the design of targeted preventative interventions that could address both behavioral and biological vulnerabilities among patients undergoing HSCT and caregivers. Our biopsychosocial model of health summarized in Fig. 1 provides guidance on the important risk and protective factors that may shape the way that HSCT impacts the aging of both caregivers and MM care recipients. Indeed, contextual factors such as demographic background, relationship quality, and both individuals' premorbid mental and physical health are important to capture, and provide opportunities for tailored interventions. Studies in the context of MM and HSCT provide the unique opportunity to look at how both the patient's and the partner's mental health may influence the trajectory of immune system reconstitution and immune system biological aging, augmenting other psychoneuroimmunology research that has addressed general immune function. This work is particularly important as the therapeutic landscape changes in multiple myeloma. Novel cellular therapy such chimeric antigen receptor T cell (CAR-T) is approved for patients with relapsed multiple myeloma, after the fourth line of therapy. Although CAR-T is increasingly being studied in earlier lines of therapy in clinical trials, our work in psychoneuroimmunology will serve as a primer for how MM HSCT (current standard of care) contrasts with that of CAR-T.

Biomarkers of aging hold promise for providing a rapid quantitative method for measuring physiologic fitness and also predicting life expectancy (Hubbard et al., 2014; Walston, 2014; Pustavoitau et al., 2016). There are a number of clinical scenarios in which biologically younger people could be prescribed more intensive therapies, with potential for greater benefit, by using a personalized cancer therapy approach based on the quantification of physiologic reserve. This approach would avoid the undertreatment of older adults with cancer due to a fear of adverse toxicities while simultaneously identifying individuals at greater risk of morbidity and mortality from aggressive therapy. Aging biomarkers may also serve as prognosticators for more aggressive cancers (Shen et al., 2020; Muss et al., 2020). Cancer-related accelerated aging research, although still sparse, has the potential to help physicians provide more tailored treatment and potentially add antiaging agents that might slow the aging trajectory and improve quality of life (Wang et al., 2021).

CRediT authorship contribution statement

Lisa M. Christian: Writing – review & editing, Writing – original draft, Supervision, Resources, Methodology, Conceptualization. **Janice K. Kiecolt-Glaser:** Writing – original draft, Supervision, Resources, Methodology, Funding acquisition, Data curation, Conceptualization. **Steve W. Cole:** . **Christin E. Burd:** Writing – review & editing, Writing – original draft, Funding acquisition, Conceptualization. **Annelise A. Madison:** Writing – review & editing. **Stephanie J. Wilson:** Writing – review & editing. **Ashley E. Rosko:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Funding acquisition, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

Acknowledgements

Preparation of this manuscript was supported by the Ohio State University Pelotonia Institutional Research Program (Project number GR12676; Rosko/Christian Co-PI).

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