**ORIGINAL PAPER** Curr Probl Psychiatry, Vol. 26(2025):73-84

DOI:10.12923/2353-8627/2025-0007

Czasopismo indeksowane na liście MNiSW - 70 pkt.

# Differences in cognitive functioning between older and younger people with multiple myeloma

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**Abstract**

**Introduction:** The aim of the study was to illustrate the difference in how multiple myeloma and its treatment affect the cognitive functioning of both older and younger patients.

**Material and methods:** The study involved the use of selected neuropsychological methods, i.e., experimental trials based on the *Battery of Tests for Assessing Cognitive Functions* PU1 and the Choynowski's *Memory Scale*.

**Results:** The interaction of health status and age appeared to be a differentiating factor between subjects under and over 65 years of age. Younger people with multiple myeloma displayed poorer performance in direct auditory memory compared to subjects of the same age without a cancer diagnosis. Similarly, regarding long-term verbal memory, patients in middle adulthood showed inferior performance in verbal memory as compared to those without multiple myeloma. Phonemic and semantic verbal fluency levels were also lower across some indicators in younger patients compared to older people with plasma cell myeloma. Better task performance by younger patients subjects with cancer was only noticeable in terms of short-term visual memory.

**Discussion and conclusions:** Decreased cognitive functioning in the middle adulthood group was associated with a worse disease course. Although the disease progresses rapidly and is detected at an advanced stage, but this does not translate negatively into patient survival, which results from a good response to treatment, mainly bone marrow transplantation. The younger age group is also subjected to more aggressive forms of treatment, known as high-dose chemotherapy, which may be associated with their poorer condition and diminished mental and physical condition.

*Keywords*: memory, medical neuropsychology, chemobrain

**Streszczenie**

**Wstęp:** Celem badania było ukazanie różnic w funkcjonowaniu poznawczym starszych i młodszych dorosłych z diagnozą szpiczaka mnogiego na skutek choroby nowotworowej i jej leczenia.

**Materiał i metoda:** Zastosowano wybrane narzędzia i metody neuropsychologiczne: próby eksperymentalno-klinicznie bazujące na *Baterii diagnozy funkcji poznawczych* PU1oraz *Skali Pamięci* Choynowskiego.

**Wyniki:** Interakcja stanu zdrowia i wieku okazała się czynnikiem różnicującym osoby badane poniżej i powyżej 65 r. ż. Młodsze osoby ze szpiczakiem mnogim mają gorszą sprawność bezpośredniej pamięci słuchowej w porównaniu do osób w tym samym wieku bez diagnozy nowotworu. Podobnie w zakresie długotrwałej pamięci werbalnej pacjenci w okresie średniej dorosłości przejawiali gorszą jej efektywność w porównaniu do osób bez szpiczaka mnogiego. Również poziom fluencji werbalnej głoskowej i semantycznej był niższy w obrębie niektórych wskaźników u młodszych chorych w porównaniu do osób starszych ze szpiczakiem plazmocytowym. Lepsze wykonanie zadań przez osoby młodsze z nowotworem zauważalne było wyłącznie w zakresie krótkotrwałej pamięci wzrokowej.

**Dyskusja i wnioski:** Obniżenie funkcjonowania poznawczego w grupie osób w okresie średniej dorosłości związane było z gorszym przebiegiem choroby nowotworowej. U osób młodszych, choroba ta gwałtownie się rozwija, wykrywana jest w zaawansowanym stadium, jednak nie przekłada się to negatywnie na przeżycie chorych, ze względu na dobrą odpowiedź na leczenie, głównie przeszczep szpiku. Młodsza grupa wiekowa pacjentów poddawana jest również bardziej agresywnym formom leczenia tzw. chemioterapii wysoko dawkowej, co może wiązać się z ich gorszym stanem i osłabioną kondycją psychofizyczną.

*Słowa kluczowe*: pamięć, neuropsychologia medyczna, chemobrain

**Introduction**

Referring to the data from the Maria Sklodowska-Curie National Research Institute of Oncology in Warsaw, Poland, the overall incidence of multiple myeloma (MM), in 2018, was 1,583, of which 777 were men and just over 800 were women. This data translates to approximately 0.9% of cases in the male population and 1% of cases in the female population against all new cancer cases in Poland [1]. Preliminary analyses of NHF data for 2016 show approximately 2,000 newly diagnosed MM patients per year, of whom more than 1,600 have started treatment [2]. Most diagnosed individuals (90%) are over 50 years of age, with the average age at diagnosis oscillating at the level of 70 years [3, 4, 2].

Most multiple myeloma cases occur in older people. The risk of cancer increases proportionally with age, starting in the 6th decade of life and reaching a the peak incidence after the age of 80 [5].

In light of contemporary research, cytokine dysregulation is one of the most significant factors influencing the occurrence of cognitive changes resulting from oncological treatment [6, 7].

The changes in the cytokine level are not homogenous in all oncological patients, but the studies confirm their relationship with the occurrence of cognitive dysfunctions [8, 9]. It was demonstrated that the administration of chemotherapy to the patients causes the increase of the cytokine level, i.e. TNF-α, IL-6, IL-8, IL-10 which, in turn, cause cognitive changes [10, 11]. It is assumed that the varied cytokine level may initiate changes in the neurotransmitter systems and the neuronal integrity through, among others, the modification of the functioning of the monoaminergic neurotransmitter system, gamma-aminobutyric acid (GABA), acetylcholine, neuropeptides, and brain-derived neurotrophic factor (BDNF). These compounds are directly related to one's cognitive state and neurodegenerative processes [12].

The research shows the relationship between the level of proinflammatory cytokines and cognitive deficits in patients with various types of cancers [8, 13]. For example, Shelli Kesler et al. and associates confirmed in their neuroimaging research the relationship between the smaller volume of the left hippocampus and the increase of TNF-α, the lower level of IL-6 and worse verbal memory in convalescents with breast cancer after completed chemotherapy [14]. In another report - by Debra E. Lyon et al., and associates from 2016, - the varied influence of cytokines on cognitive variables including executive functions was also demonstrated in women with breast cancer undergoing adjuvant chemotherapy. The IL-10 was negatively correlated with cognitive flexibility and visual memory six months after the start of chemotherapy. When it comes to the IL-6, its level during the treatment was greatly changing, - starting with from the sudden increase approximately half of a year after the beginning of chemotherapy, until sudden drop below the baseline level 24 months later. Additionally, the significant negative relationship between attention and this cytokine was noticed a year after receiving the first dose of treatment [15].

On the basis of the above research it can be concluded that there is a significant contribution of cytokines on to the development of cognitive disorders in cancer patients. Cognitive disorders, which arised as a result of cancer and oncological treatment also occur in case of patients with plasma cell myeloma [16]. A varied cytokine level can be one of the etiological factors of the cancer and cognitive disorders, that takes place in multiple myeloma [17, 18].

Cytokines and growth factors synthesized by bone marrow cells or bone marrow stromal cells as a consequence of intercellular interactions give rise to the multiplication and the activity of osteoclasts and the proliferation of multiple myeloma cells, as well as to the process of angiogenesis [19].

In the case of MM, targeted therapy is directed at cytokines, such as interleukin-6, interleukin-10 and tumor necrosis factor TNF-α, since it is observable that these biological factors are heavily involved in cancer progression [20].

The IL-6 is a key growth and survival factor of multiple myeloma cells. This cytokine plays a crucial role in the development of MM due to its influence on growth regulation and survivability of cancer cells. On the basis of research by Artur Jurczyszyn et al., from 2014, and associates (2014) it was concluded that the concentration of, for example, the IL-6 and the sIL-6R in blood plasma was significantly higher in patients with MM as in comparison with the control group. Depending on its duration, anti-cancer therapy effectively lowered the concentration of the cytokine and its receptors [19].

The concentration of the IL-6 and the sIL-6R receptor in blood plasma remain elevated and correlate with the advanced stage of the oncological process [21, 22] in the group of multiple myeloma patients. The IL-6 production by bone marrow stromal cells is stimulated by the TNF-α, among others [23]. Significantly higher concentration of the IL-6 in the blood serum of patients with multiple myeloma and further increase of its concentration along with the progression of this cancer were also observed

[24]. Additionally, the tumor necrosis factor inhibits the differentiation of osteoblasts *in vitro* [25].

In case of multiple myeloma, the IL-10 induces both the proliferation of plasma cells and angiogenesis [17], so it influences the stage of the neoplastic process [26]. Reports from 2016 [27] confirm that the concentration of IL-10 in the blood serum of MM patients was significantly increased when compared with healthy people. Considerably elevated levels of IL-10 in blood serum were correlated with the clinicopathological features of the cancer in MM patients. Additionally, the increased concentration of the IL-10 was related to patients' weak reactions to the treatment. Taking into consideration the relationship between the IL-10 and other cytokines, it can be shown that the IL-6 leads to the production of the IL-10 and that it constitutes a the growth factor for the multiple myeloma cells correlated with the IL-6. This fact entails important practical implications for MM treatment methods [28].

In case of hematologic cancers such as MM, bone marrow transplantation constitutes one form of treatment which may cause changes in the cognitive functioning of patients [29, 30]. Among the possible causes of cognitive dysfunctions resulting from transplantation one can specify simultaneous administration of both chemotherapy and irradiation prior to the transplantation, the graft-versus-host disease as well as treatment with the use of steroids [31]. In their reports, Desiree Jones et al. and associates confirmed the existence of the dysfunctions of memory and executive functions in patients diagnosed with multiple myeloma after bone marrow transplantation [16]. On the other hand, in the longitudinal study by Sheri R. Jacobs and her team, in which 63% of the study group consisted of the patients with multiple myeloma, it was observed that the cognitive functioning of the patients improves a year after the bone marrow transplantation, which is why chemobrain may be considered transient phenomenon [32].

The source literature shows that cancer and undergoing treatment are not the only elements contributing to cognitive changes in MM patients. The age of the study participants subjects may be one among of the unfavorable prognostic factors. Referring to the genetic origin of MM, subsequent cases were diagnosed at an earlier age in younger generations of families with multiple myeloma. Patients in the younger age group (21–40 years) were found to have a higher prevalence of osteolysis and high-risk cytogenetic abnormalities than older patients, which may indicate a worse course of the disease in younger patients compared to those in late adulthood [33]. Hence, the important role of age at onset and manifestation of symptoms is inferred.

**Material and methods**

The following research problem was formulated: Do and how do age and cancer differentiate the cognitive functioning of the studied subjects, or if so, how? The following research hypothesis is related to the presented problem: The presence of cancer and age will differentiate the cognitive functioning of the studied subjects.

*Participants*

The study group included 30 (13 male and 17 female) newly diagnosed MM patients who received first-line chemotherapy. Patients were recruited in the Department of Hematooncology and Bone Marrow Transplantation. The diagnosis of MM diagnosis was based on SLiM CRAB criteria [2, 4], according to the International Myeloma Working Group (IMWG) recommendations. The control group consisted of 30 individuals, with no cancer diagnosis. These were the patients of the Rehabilitation Department, who participated in a daily rehabilitation program. The control group was recruited to create same-sex pairs characterized by similar age (difference of 2-3 years) and education, so as to control the impact of these side variables as much as possible.

Table 1 contains the information about the selected demographic variables.

The data (table 1) indicate a minor advantage of the number of women over men in each group. The group, which was the biggest in size, consisted of people with secondary education with matriculation certificate exam. The study participants were aged between in the age range of 49 and to 78 years. The participants' age deviated from the mean by approximately 7-8 years

The next table (2) shows the chemotherapy and the adjuvant therapy type that were administered to the oncological patients.

On the basis of the data presented, one it can be assumed that MM patients constituted a diverse group when it comes to the type of the chemotherapy received. Bortezomib was the only cytostatic received by all of the participants.

In terms of adjuvant therapy, the majority of the studied patients received pamidronate disodium. More than ¼ a quarter of the patients were subjected to the treatment with zoledronic acid. The smallest percentage of the patients consisted of people without the adjuvant treatment (about 17%).

The procedure was interrupted several times because of restricted access to recruiting recruitment of new patients in the Covid-19 pandemic. The hospital was a two-time lock-down twice of the hospital with a subsequent restriction of visits. Another factor was an increased number of influenza cases and the inability to conduct the study in the hospital. The group of 30 patients

*Table 1. Characteristics of the study group – sex, education, age*

| Demographic variables | Categories / Descriptive statistics | Group | | | |
|---|---|---|---|---|---|
| | | Clinical | | Control | |
| | | *N* | *%* | *N* | *%* |
| **Sex** | Female | 17 | 56.7 | 17 | 56.7 |
| | Male | 13 | 43.3 | 13 | 43,3 |
| **Education** | Elementary | 5 | 16.7 | 5 | 16.7 |
| | Vocational education | 8 | 26.7 | 8 | 26.7 |
| | Secondary education | 13 | 43.3 | 13 | 43.3 |
| | Higher education | 4 | 13.3 | 4 | 13.3 |
| **Age (years) – at the time of diagnosis for the clinical group** | *M* | 65.7 | | 65.6 | |
| | *SD* | 7.96 | | 7.12 | |
| | *Min.* | 49 | | 52 | |
| | *Max.* | 78 | | 76 | |

*Note. M – Mean; SD - Standard Deviations; Min. – Minimum; Max. – Maximum.*

*Table 2. Characteristics of the study group in terms of the type of chemotherapy and adjuvant therapy received*

| | **N** | **%** |
|---|---|---|
| **Chemotherapy type** | | |
| VCd – bortezomib, cyclophosphamide, dexamethasone | 12 | 40 |
| VTd – bortezomib,thalidomide, dexamethasone | 17 | 56.7 |
| Vd – bortezomib, dexamethasone | 1 | 3.3 |
| **Adjuvant therapy type** | | |
| Pamidronate disodium | 17 | 56.7 |
| Zoledronic acid | 8 | 26.7 |
| No adjuvant therapy | 5 | 16.7 |

was selected according to the inclusion criteria was and successfully recruited during the 6 years of the study. The reasons for the reduction of the initial, 81-person, study group were: study discontinuation, death, change of treatment center, anemia, poor overall physical and mental health. The 30-person control group, which consisted of 30 patients, was recruited for the criterion group to create pairs.

The exclusion criteria for the clinical and control group were as the following: other active oncological, neurological, or psychiatric diseases, and asevere anemia on the day of the examination that could have an indirect influence on fatigue and cognitive functions. The decision to include patients in the criterion and control group was made on the basis of documentation and patient interview (no history of treatment or administration of and taking oncological, neurological, psychiatric medication confirmed on the basis of medical and psychological documentation and in interview with the patient). Patients who were observed to be anemic diagnosed with anaemia before the recruitment diagnosis were given initial treatment – correction of anemia, e.g., blood transfusion.

**Measures**

The tools used in the research are in line with the evidence-based psychological practice (EBPP). These included:

1. Battery of Tests for Assessing Cognitive Functions PU1 – a comprehensive tool for the assessment of memory, attention, and executive functions in children and youth aged 10-12 by Aneta R. Borkowska, Urszula Sajewicz-Radtke, Małgorzata Lipowska, and Dorota Kalka [34]. In the present study, the PU1 battery was used in an experimental way. The subjects' scores were not recalculated and compared to norms, – as only the raw score was analyszed. It was decided to use PU1 Battery in an experimental way, because during the creation of the research schedule and during the selection of the research tools, there were no neuropsychological diagnostic tools available on the market which would allow to examine a patient's several executive functions in a short, complex and non-burdensome way. Pilot studies involving a group of healthy participants and those who were diagnosed with

cancer showed that these tools are adequate for the diagnosis of adults as they did not formulate any remarks regarding the difficulty level of the presented tasks as too low. The following subtests were selected:

- Deferred Naming Test (DNT), assessing working memory.
- Verbal fluency I (VFI) and Verbal fluency II (VFII), assessing phonemic and semantic fluency [34].

2. Experimental and clinical trials based on the Choynowski's Memory Scale, which is based on the assumptions of the classic scale for assessing mnestic functions – Wechsler Memory Scale. According to the author, this Scale, is helpful in assessing memory in healthy individuals and is also intended for clinical diagnosis [35]. In the author's own research, the following subtests of the Scale were used:
   - Verbal memory – a subtest allowing for the assessment of short-term memory.
   - Long-term memory – a subtest assessing delayed memory [35].

**Procedure**

The research was conducted on the premises of at the Department of the Hemato-oncology and Bone Marrow Transplantation Clinic. The study protocol was approved by the Bioethics Committee (no. KE-0254/253/2016). All study participants signed written consent to take part in the research. The procedure involving 30 patients with multiple myeloma was conducted before chemotherapy. The study was performed between the diagnosis of multiple myeloma and the beginning of chemotherapy treatment (with no more than one month between the diagnosis and the beginning of the treatment). The criterion control group was examined one time.

**Data Analyses**

The analyses were performed using the IBM SPSS Statistic version 26.0. The research hypothesis concerned the variation of cognitive function levels caused by cancer and the age of the participants. A Two-way ANOVA 2x2 analysis of variance was used to the test it of this hypothesis. It was found that the distribution of the studied variables did not differ significantly from the normal distribution. The variances were homogeneous and the sizes of the individual groups were similar, hence the conditions for parametric two-factor way analysis of variance in a 2 x 2 design were met. The f Factors, which were considered were included age (younger people – up to and including 65 years of age and older people – over 65 years of age) and health status (cancer patients – clinical group and people without cancer diagnosis – control group). On this basis, 4 subgroups were identified: younger patients with a cancer diagnosis ($N$ = 13) and older patients with multiple myeloma ($N$ = 17), as well as younger subjects without a cancer diagnosis ($N$ = 14) and older individuals also without a cancer diagnosis ($N$ = 16).

**Results**

Table 3 shows the basic descriptive statistics for the cognitive variables (direct auditory memory, short-term visual memory, long-term verbal memory, phonemic and semantic verbal fluency) regarding the age and health status (type of the group: clinical or control) of the subjects.

The data in the table 3 shows similar mean scores in direct auditory memory performance among subjects in late adulthood (over 65 years of age). The highest mean was noted in young people without a cancer diagnosis, while the lowest in cancer patients in middle adulthood (up to 65 years of age). This shows a trend towards lower short-term visual memory scores in younger multiple myeloma patients in comparison to with the remaining three subgroups. Descriptive statistics also indicate low mean scores among the older people subjects without cancer, as well as among younger cancer patients (up to age 65), in terms of long-term verbal memory. The range of scores across the four subgroups studied was 9-11 points. The difference was also found between the non-cancer group and patients with a multiple myeloma diagnosis. The results deviated from the mean at a similar level in four identified groups regarding verbal phonemic fluency. Referring to the descriptive statistics in terms of the indicators of semantic verbal fluency, it can be inferred that a higher number of switches were made by patients with cancer as compared to individuals without a diagnosis in the younger group. Regarding the older studied group, a higher average of switches was presented by non-cancer subjects without the disease than by those with a multiple myeloma diagnosis. The greatest diversity in the obtained results was seen among cancer patients under 65 years of age ($SD$ – 4.3).

To test whether the observed differences were statistically significant, a two-way analysis of variance was conducted in a 2 x 2 design. The data is shown in table 4.

The two-factor way analysis of variance revealed significant differences in direct auditory memory. The interaction effect between health status and age was found to be statistically significant ($F$ = 5.5; $p$ = 0.023). It explained 9% of the variability in performance indirect auditory memory.

Significant differences in short-term visual memory were also found. The interaction effect between health status and age proved statistically significant ($F$ = 5.9;

*Table 3. Descriptive statistics for the indicator of cognitive variables with with reference to age and health status*

| Variable | Indicator | Health factor | Age factor | *M* | *SD* | *Min.* | *Max.* |
|---|---|---|---|---|---|---|---|
| **Direct auditory memory** | Point score *Auditory memory* | Cancer diagnosis (Clinical group) | Younger | 4.8 | 2.4 | 1 | 9 |
| | | | Older | 5.8 | 2.1 | 1 | 9 |
| | | No cancer (Control group) | Younger | 8.1 | 3.5 | 3 | 13 |
| | | | Older | 5.4 | 3.8 | 0 | 13 |
| **Short-term visual memory** | Number of restarts DNT | Cancer diagnosis (Clinical group) | Younger | 4.3 | 2.3 | 1 | 9 |
| | | | Older | 6.4 | 2.2 | 2 | 10 |
| | | No cancer (Control group) | Younger | 6.1 | 2.3 | 3 | 9 |
| | | | Older | 5.1 | 2.6 | 2 | 9 |
| **Long-term verbal memory** | Point score *Long-term memory* | Cancer diagnosis (Clinical group) | Younger | 3.4 | 2.6 | 0 | 10 |
| | | | Older | 5.2 | 2.3 | 2 | 11 |
| | | No cancer (Control group) | Younger | 6.9 | 3.9 | 1 | 12 |
| | | | Older | 3.1 | 3 | 1 | 10 |
| **Phonemic verbal fluency** | Number of switches *Verbal fluency I* | Cancer diagnosis (Clinical group) | Younger | 8.1 | 3.7 | 3 | 16 |
| | | | Older | 6.1 | 3.8 | 0 | 15 |
| | | No cancer (Control group) | Younger | 6.8 | 2.2 | 4 | 10 |
| | | | Older | 8.1 | 2.5 | 4 | 12 |
| **Semantic verbal fluency** | Number of switches *Verbal fluency II* | Cancer diagnosis (Clinical group) | Younger | 7.2 | 4.3 | 1 | 18 |
| | | | Older | 5 | 2.2 | 0 | 9 |
| | | No cancer (Control group) | Younger | 4.8 | 2.3 | 1 | 8 |
| | | | Older | 6.5 | 1.8 | 4 | 10 |

*Note. M – Mean; SD - Standard Deviations; Min. – Minimum; Max. – Maximum; DNT – Deferred Naming Test.*

*Table 4. F statistics for main effects and interaction effect for cognitive variables in two-way analysis of variance*

| Variable | Indicator | Source | *F* | *p* | Partial $\eta^2$ |
|---|---|---|---|---|---|
| **Direct auditory memory** | Point score *Auditory memory* | Health status | 3.44 | 0.069 | 0.06 |
| | | Age | 1.01 | 0.32 | 0.02 |
| | | Health status * Age | 5.5* | 0.023 | 0.09 |
| **Short-term visual memory** | Number of restarts DNT | Health status | 0.14 | 0.708 | 0.003 |
| | | Age | 0.68 | 0.413 | 0.01 |
| | | Health status * Age | 5.9* | 0.018 | 0.1 |
| **Long-term verbal memory** | Point score *Long-term memory* | Health status | 0.78 | 0.382 | 0.01 |
| | | Age | 1.68 | 0.2 | 0.03 |
| | | Health status * Age | 13.52*** | 0.001 | 0.19 |
| **Phonemic verbal fluency** | Number of switches *Verbal fluency I* | Health status | 0.19 | 0.664 | 0.003 |
| | | Age | 0.21 | 0.651 | 0.004 |
| | | Health status * Age | 4.1* | 0.048 | 0.07 |
| **Semantic verbal fluency** | Number of switches *Verbal fluency II* | Health status | 0.37 | 0.543 | 0.01 |
| | | Age | 0.1 | 0.758 | 0.002 |
| | | Health status * Age | 7.43** | 0.009 | 0.12 |

*Note. F –Fisher test; p - probability value; η2-eta-squared; DNT– Deferred Naming Test. *p < 0.05, **p < 0.01, ***p < 0.001*

$p = 0.018$). It explains approximately 10% of the variance in the dependent variable. It was a moderately strong effect.

The two-way analysis of variance also revealed significant differences in long-term memory. The interaction effect between health status and age was found to be statistically significant ($F = 13.52$; $p = 0.001$). It explained 19% of the variability in long-term auditory

memory scores. It was a strong effect.

Referring to the subsequent data in table 4, it can be concluded that the two-way analysis of variance showed significant differences in one indicator of phonemic verbal fluency – the number of switches. The interaction effect between health status and age was found to be statistically significant ($F$ = 4.1; $p$ = 0.048). It explained 7% of the variation in performance in terms of the ability to move from one group of words to another when listing those starting with the 'k' sound.

The two-way analysis of variance revealed significant differences in semantic verbal fluency in terms of the number of switches. The interaction effect between health status and age was found to be statistically significant ($F$ = 7.43; $p$ = 0.009). It explained approximately 12% of the score variation in performance within the ability to move from one group of words to another when naming animals within 1 minute. It was a strong effect. To better illustrate the interaction effect, subsequent comparisons between pairs were conducted.

In the table 5 there is the interaction effect between age and health status revealed differences in direct auditory memory performance between younger and older patients subjects in the group without a cancer diagnosis ($p$ < 0.05). People in middle adulthood reproduced the text they heard directly more faithfully compared to older individuals (over 65 years of age) in the healthy group (without cancer).

*Table 5. Pairwise comparison for the age x health status interaction effect, with reference to the variable measures - direct auditory memory, short-term visual memory, long-term verbal memory, phonemic verbal fluency, semantic verbal fluency - on two age levels*

| Variable | Health status | Age (I) | Age (J) | Mean difference (I-J) | *p* |
|---|---|---|---|---|---|
| **Direct auditory memory** | No cancer | Younger | Older | 2.63* | 0.021 |
| | Cancer diagnosis | Younger | Older | -1.05 | 0.349 |
| **Short-term visual memory** | No cancer | Younger | Older | 1.01 | 0.26 |
| | Cancer diagnosis | Younger | Older | -2.05* | 0.026 |
| **Long-term verbal memory** | No cancer | Younger | Older | 3.87*** | 0.001 |
| | Cancer diagnosis | Younger | Older | -1.85 | 0.099 |
| **Phonemic verbal fluency** | No cancer | Younger | Older | -1.28 | 0.272 |
| | Cancer diagnosis | Younger | Older | 2.02 | 0.087 |
| **Semantic verbal fluency** | No cancer | Younger | Older | -1.71 | 0.092 |
| | Cancer diagnosis | Younger | Older | 2.15* | 0.037 |

*Note. *p < 0.05, ***p < 0.001*

The interaction effect between age and health status revealed differences in short-term visual memory between younger and older people in the group diagnosed with multiple myeloma ($p$ < 0.05). People in middle adulthood (younger) with cancer were characterized by significantly fewer restarts, meaning that they reproduced longer sequences of shown and remembered images compared to older patients (aged over 65).

It can be concluded that the interaction effect between age and health status revealed differences within the deferred verbal memory between younger and older people in the group without a cancer diagnosis ($p \leq 0.001$). Patients in middle adulthood reproduced the text they heard and stored in the long-term memory store more faithfully compared to older subjects (over 65 years of age) in the healthy group (without cancer).

A comparison between pairs proves that the interaction effect between age and health status revealed differences in the number of switches in phonemic fluency between younger and older people in the group with a cancer diagnosis only at the level of statistical tendency ($p$ = 0.087).

The data in the table 5 indicate that an interaction effect between age and health status revealed differences within the number of switches in semantic fluency between younger and older people in the group of those study participants with a cancer diagnosis ($p$ < 0.05). Patients with multiple myeloma in middle adulthood used more switchers compared to older subjects (over 65 years of age).

Further comparisons, presented in the table 6, allow us to conclude that the interaction effect between age and the presence or absence of oncological disease showed statistically significant differences in the ability to repeat directly heard verbal material between healthy and ill patients in the age group aged less than 65 years ($p$ < 0.01). Younger people with a multiple myeloma diagnosis remembered and reproduced less of the information they directly heard compared to subjects participants in the same age group without a cancer diagnosis.

Further analyses allow us to conclude that health status did not differentiate short-term visual memory among both in either younger and or older individuals subjects. It is possible to notice a result at the level of

*Table 6. Pairwise comparison for the age x health status interaction effect, with reference to the variable measures - direct auditory memory, short-term visual memory, long-term verbal memory, phonemic verbal fluency, semantic verbal fluency - on two levels of health status*

| Variable | Age | Health status (I) | Health status (J) | Mean difference (I-J) | *p* |
|---|---|---|---|---|---|
| **Direct auditory memory** | Younger | No cancer | Cancer diagnosis | 3.3** | 0.006 |
| | Older | No cancer | Cancer diagnosis | -0.39 | 0.716 |
| **Short-term visual memory** | Younger | No cancer | Cancer diagnosis | 1.76 | 0.064 |
| | Older | No cancer | Cancer diagnosis | -1.29 | 0.132 |
| **Long-term verbal memory** | Younger | No cancer | Cancer diagnosis | 3.54** | 0.003 |
| | Older | No cancer | Cancer diagnosis | -2.17* | 0.042 |
| **Phonemic verbal fluency** | Younger | No cancer | Cancer diagnosis | -1.29 | 0.291 |
| | Older | No cancer | Cancer diagnosis | 2 | 0.073 |
| **Semantic verbal fluency** | Younger | No cancer | Cancer diagnosis | -2.37* | 0.028 |
| | Older | No cancer | Cancer diagnosis | 1.5 | 0.121 |

*Note. *p < 0.05, **p < 0.01*

statistical tendency ($p = 0.064$), which, with an increase in the size of the study group, could emphasize the existence of differences in one of the indicators of the dependent variable resulting from the health status among people in middle adulthood.

The results of further analyses indicate that the interaction effect between age and the presence or absence of oncological disease showed statistically significant differences in the deferred reproduction of verbal material between healthy and ill participants subjects in the group aged less than 65 years ($p \leq 0.01$). Young adults with a multiple myeloma diagnosis remembered and retrieved less information heard and stored in long-term memory compared to subjects in the same age group without a cancer diagnosis. Within the group of older participants, differences were also observed at the level of statistical significance within selected mnestic memory functions between ill and healthy subjects ($p < 0.05$). Older people without a cancer diagnosis were characterized by paradoxically lower long-term memory performance compared to those of the same age with multiple myeloma.

Subsequent analyses allow us to conclude that the interaction effect between age and the presence or absence of oncological disease showed differences at a level close to one that is statistically significant ($p = 0.073$) in terms of the number of switches between the healthy and ill in the group of individuals over 65 years of age.

Referring to subsequent comparisons between pairs (see the table 6.), it is possible to ascertain that the interaction effect between age and the presence or absence of oncological disease showed statistically significant differences in the number of switches between healthy and ill subjects in the age group aged less than 65 years ($p < 0.05$). Younger individuals with a diagnosis of multiple myeloma used more switches compared to subjects in the same age group without a cancer diagnosis.

**Discussion and conclusions**

Considering the results of the author's own study, the hypothesis: "The presence of cancer and age differentiate the cognitive functioning of the study subjects participants" was partially confirmed. Both age and health status played a role in differentiating the cognitive functioning of patients, with their interaction also being a significant factor. The greatest number of changes resulting from age and health status were observed with selected memory and attention processes and verbal fluency.

As for memory, considering the interaction of age and health status, younger people with multiple myeloma performed worse on the *Auditory memory* test than those without a cancer diagnosis in the same age group. This can probably be explained by the more acute and worse course of the cancer disease in younger people compared to those with the disease at the typical age for myeloma, i.e., in the 6$^{th}$ or 7$^{th}$ decade of life.

Similarly, differences were registered in short-term visual memory within the number of restarts (task *Deferred naming test*). It turned out that younger subjects patients with cancer functioned better in terms of short-term visual memory compared to older patients subjects with a cancer diagnosis. The research conducted by Barbara Eberhardt and team found similar relationships. They examined patients with hematologic and gastrointestinal cancers, divided into a group of younger subjects, who were (up to 60 years of age) and the group of older subjects, so those over 60 years of age. Cognitive impairment of memory (measured by *Sydrom-Kurztest* and its subtests – *Naming Objects, Delayed Recall, Recognition Memory*, checking i.a. the functioning of short-term visual memory) was noted in the group of patients who were at least in the 7$^{th}$ decade of life compared to individuals

aged less than 60 years, soon after the beginning of chemotherapeutic treatment [36].

Another aspect of memory in which age and health status significantly contributed to the differentiation of subjects was long-term verbal memory. As for younger individuals with a cancer diagnosis, they functioned worse than participants subjects of the same age without multiple myeloma. In contrast, inverse relationship was noticed in the older group with plasma cell myeloma. Older patients subjects with a cancer diagnosis performed better at recalling information from the text told at the beginning of the test than patients in the control group – with locomotive dysfunctions. Reports from 2014 by Juan A. Cruzado et al. and associates, which involved a group of subjects with colorectal cancer, presented a statistically significant decrease in verbal memory performance, both immediate and deferred, after chemotherapy, with the simultaneous return of lost functions six months after the last treatment cycle. The authors of this research emphasize that it is very difficult to indicate the cause of the emerging dysfunctions unequivocally (presence of deficits before treatment, lower cognitive reserve, and advanced age $M$ = 66.96) [37], which confirms the heterogeneous nature of cancer-related cognitive impairment (CRCI) that also emerges in our study.

In terms of the number of switches in phonemic and semantic verbal fluency, the subjects were diversified due to the interaction of age and health status. It is concluded that younger people with a diagnosis of multiple myeloma were characterized by a greater tendency to switch from one word group to another as compared to people over 65 also with a cancer diagnosis. The data available in literature indicates that the ability to produce words within phonemic and semantic fluency, (starting with the 'k' sound), as well as the ability to form clusters in semantic fluency tasks and phonemic clusters decrease with age. Older age also correlates with fewer semantic and phonemic switches in both types of verbal fluency [38]. The impact effect of age on verbal fluency was noticeable in the authors' own study as well.

Older patients subjects (over 65) without a cancer diagnosis, who participated in this study had more switches when tested for phonemic fluency compared to those with the disease. In regard to the number of switches when tested for semantic fluency, younger multiple myeloma patients had a higher rate of them compared to those of the same age without a cancer diagnosis. Higher switch rates in sentences measuring phonemic and semantic verbal fluency may indicate more effective information extraction and the use of efficient recalling strategies. Referring to studies, which assessed neutral and affective fluency in patients with damage to the right, left, or both hemispheres of the brain, it was found that, for sentence switching given switches, people with CNS pathology used switches (congruent and incongruent with the criterion) from one to another word group less frequently than healthy people [39].

The lack of differences distinguished by the interaction of health status and age was noticeable within such variables as general cognitive functioning, working memory, planning, and executive control. There are also available reports confirming the lack of differences in cognitive functioning in the older population with a cancer diagnosis [40].

Summarizing the results of the analyses conducted in connection with the hypothesis, it is possible to observe emerging relationships. One of them is associated connected with the decline in of functioning in of older patients with cancer, while the other notes the deterioration of cognitive processes in patients in middle adulthood. When it comes to older individuals with a cancer diagnosis, the literature states that there are mutual interactions between aging and the cancer process. For example, oxidative stress is among the causes of CRCI, and it is one of the etiological variables affecting the aging process [41]. Advanced age is a risk factor for the onset of oncological disease [42, 43], while the onset of cancer and related treatment can accelerate the aging process [44, 45]. There are two hypotheses to explain the impact of cancer on the aging process. One involves a normal aging trajectory with a weakened cognitive reserve (a parallel, reduced course compared to the typical aging process), and the other of a faster and sharper trajectory with a tendency toward progression and deterioration of the functional status [46, 47]. In the authors' own research, it was observed that older cancer patients recalled shorter sequences of shown images compared to healthy people, which would confirm the negative impact of the interaction of age and cancer on short-term visual memory. Similarly, in a study by Arti Hurria and associates [48], it was found that older breast cancer patients experienced deterioration in cognitive functioning, i.a., in terms of visual memory, as a result of adjuvant chemotherapy.

Another trend emerging in relation to the hypothesis is that the younger group, (before age 65,) functions worse in selected cognitive domains, i.e. direct auditory memory and long-term verbal memory. Decreased cognitive functioning in the middle-old adulthood group was associated with a worse disease course in younger people, while it is customary for multiple myeloma to occur later, namely in the 6th-7th decade of life. When plasma cell myeloma is diagnosed earlier (in middle age adulthood), the disease progresses rapidly, is detected at an advanced stage, and patients usually suffer from renal failure, but this does not translate negatively into affect their

survival, because of a good response to treatment, mainly bone marrow transplantation [49, 50]. The younger age group of patients also undergoes more aggressive forms of treatment known as high-dose chemotherapy [51], which may be associated with poorer condition and a deterioration in the overall mental and physical state. Similar relationships regarding the dynamics of the condition are noted among patients with Alzheimer's disease, in which who early onset is associated with a genetic background, a more aggressive course, worse visuospatial performance, reduced executive functioning, attention problems, worse praxis with simultaneously less frequently manifested memory problems [52, 53]. The genetic background of chemobrain and Alzheimer's disease may have the same determinants in the form of the presence of the ε4 allele of Apolipoprotein E [54, 55].

## Limitations

The small group size could be a limitation of the conducted research. In future projects, it is also worth to controlling the variable treatment method in younger and older groups.

## Funding

This research was funded by the National Science Center in Poland, grant number 2017/27/N/HS6/02057.

## Conflict of interest

The authors have declared no conflict of interest.

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Otrzymano: 20.03.2025
Zrecenzowano: 22.04.2025, 07.06.2025, 08.07.2025
Przyjęto do publikacji: 22.08.2025