



# Cognitive impairment is related to a reduced count of T-lymphocytes in older patients diagnosed with non-small cell lung cancer (NSCLC)

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**Background:** Aging is a risk factor for cancer and cognitive impairment, and both have been related to changes in the immune system (immunosenescence) and chronic inflammation (inflammaging) of elderly individuals. Therefore, it would be interesting to know if there is a connection between immunological variations and cognitive function in oncologic patients, especially in lung cancer, in which, inflammation plays a crucial role in tumor development and progression. Our objective is to assess, in older patients diagnosed with non-small cell lung cancer (NSCLC), differences in parameters of the immune system depending on their cognitive status.

**Methods:** We retrospectively analyzed patients  $\geq 70$  years diagnosed with NSCLC with evaluated cognitive function, from January 2017 to April 2019. Lymphocyte count was gathered at baseline and checked for differences in lymphocyte counts between patients with a Pfeiffer result of 0–2 *vs.* 3–10 mistakes. Multiple regression models were used to assess the impact of clinical parameters on lymphocyte count.

**Results:** Seventy patients were analyzed. Sixty had a normal cognitive function, while ten had an impaired cognitive status; these were significantly older. Multivariate analysis showed that patients with cognitive impairment had lower levels of total, T and CD8+ T-lymphocytes ( $P=0.011$ ,  $0.011$  and  $0.019$ , respectively). Older age was only correlated to higher level of CD8+ T-lymphocytes ( $P=0.0390$ ). Odds ratio for the risk of cognitive impairment depending on the level of T-lymphocytes was  $0.996$  (95% CI:  $0.995$ – $0.998$ ),  $P=0.037$ .

**Conclusions:** T-lymphocyte count is lower in patients diagnosed with lung cancer and cognitive impairment. These findings suggest that clinical features are closely related to immunological status in older patients with NSCLC. Therefore, age cannot always explain immunosenescence, and geriatric assessment could help.

**Keywords:** Immunosenescence; non-small cell lung cancer (NSCLC); comprehensive geriatric assessment; older patients; cognitive impairment

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Submitted May 04, 2020. Accepted for publication Sep 18, 2020.

doi: 10.21037/tcr-20-1997

View this article at: <http://dx.doi.org/10.21037/tcr-20-1997>

## Introduction

Aging is a risk factor for both cancer and cognitive impairment (1,2). Furthermore, cognitive alterations have been widely studied in patients diagnosed with neoplasms, specially related to treatment with chemotherapy, as a condition globally known as chemobrain or chemofog (3,4). Despite this, the mechanisms that induce cognitive impairment in patients with cancer are not fully understood, especially in older patients, in which multiple risk factors coexist. Knowledge of associated factors to cognitive impairment in elderly patients with cancer appears to be of great importance given its higher prevalence in this population and the possible greater risk of treatments to induce or worsen cognitive damage (5).

During the last years, growing evidence of the relationship between immune alterations that occur with aging (known as immunosenescence) and neurodegenerative diseases has emerged (6,7). The hallmarks of immunosenescence are reduced response to antigens and increased number of senescent cells associated with a chronic inflammatory status (inflammaging) (8) in a highly complex process that cannot only be explained by cellular aging, but is also influenced by antigenic exposure or nutritional status among other factors. Regarding neurodegenerative diseases, chronic systemic inflammation has demonstrated to alter the permeability of the blood-brain barrier (BBB) and allow proinflammatory substances to cross the BBB and induce microglia activation and promotion of central nervous inflammation, that can cause brain damage (6,7).

Immunosenescence has also been described as one of the main hallmarks of cancer: the immune system plays a major role in tumoral surveillance; but, due to a continuous stimulation by tumoral cells, it can also induce an inflammatory state and promote cancer growth (9). That is why, recently, there has been a great development of treatments that enhance immune cells to destroy tumour cells. This is especially important in non-small cell lung cancer (NSCLC) given its relationship with inflammation and tumor development and progression (10). Furthermore, median age of diagnosis of NSCLC is around 70 years (11); that implies a higher number of patients in daily clinical

practice that, because of their age, are more prone to suffer from cognitive diseases.

Although there is a reasonable connection between brain damage, cancer development and immunosenescence; risk factors that promote cognitive impairment related to cancer in older patients and biological markers linked to immunosenescence are yet unknown. For this reason, the objective of this study is to assess, in older people diagnosed with NSCLC, if there is a statistically significant difference in lymphocyte populations depending on their cognitive status defined by the screening Pfeiffer test. We present the following article in accordance with the STROBE reporting checklist (available at <http://dx.doi.org/10.21037/tcr-20-1997>).

## Methods

### *Study design*

We performed a cross-sectional study including patients of  $\geq 70$  years diagnosed with NSCLC from January 2017 to April 2019 at Hospital Universitario Doctor Peset (Valencia, Spain). Clinical staging was defined according to the guidelines of the tumor-node-metastasis (TNM) staging system of the Union for International Cancer Control (8th Edition) (12).

Patients older than 70 years with a histopathological diagnosis of NSCLC were incorporated into the study if their analytical and clinical profiling information was available, together with the comprehensive geriatric assessment that includes the evaluation of the performance of daily living activities and instrumental daily living activities, cognitive, nutritional and emotional status, and comorbidities. Among the cases reviewed, only patients who had undergone the Pfeiffer test were considered eligible, while those previously diagnosed with an immunodeficiency, an autoimmune disease or a chronic infection (such as HIV or hepatitis) were considered ineligible. The demographic and clinicopathologic characteristics were recorded and archived in the hospital informatics system. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and it was approved by the Ethics Committee of the Hospital Universitario Doctor Peset (ID

**Table 1** Short portable mental status questionnaire (SPMSQ) or Pfeiffer screening test

- 
1. What are the date, month and year?
  2. What is the day of the week?
  3. What is the name of this place?
  4. What is your phone number?
  5. How old are you?
  6. When were you born?
  7. Who is the current president?
  8. Who was the president before him/her?
  9. What is your mother's surname?
  10. Can you count backward from 20 by 3's?
- 

local code 77/17). Written informed consent was exempted because of the retrospective nature of the study and assured anonymity.

### ***Blood samples and lymphocyte count***

During the first appointment in the Medical Oncology clinic, blood samples were obtained aseptically by venipuncture and collected in EDTA tubes to assess the lymphocyte profile during the following 2–4 hours after collection. The blood samples in the present study were collected between 9:00 and 11:00 am, in order to minimize the possible effects of circadian rhythmicity shown by certain immune cells. Lymphocyte count by flow cytometry was gathered from this blood test at baseline. Immunophenotyping included CD3<sup>+</sup>, CD4<sup>+</sup> and CD8<sup>+</sup> T-lymphocytes, B-lymphocytes and natural killer (NK)-lymphocytes. The analysis was performed in the cytometry laboratory at the Hematology Department of our hospital using a Beckman Coulter<sup>®</sup> flow cytometer and the data were reported in absolute and relative values. Moreover, the rest of hematologic and biochemistry parameters were gathered. Flow cytometry is a widely used technique, available in most hospitals, which makes it the ideal procedure to evaluate immune system in daily clinical practice.

### ***Pfeiffer test***

During the first visit in the Medical Oncology clinic a complete medical interview is performed, usually including the geriatric assessment in older patients. Comprehensive

geriatric assessment includes evaluation of cognitive status using the short portable mental status questionnaire (SPMSQ) or Pfeiffer test in the patient's mother tongue, as recommended by the Working Group on Oncogeriatrics of the Spanish Society of Medical Oncology (13). This is a validated and reproducible tool to evaluate cognitive status in older patients, composed of 10 items listed in *Table 1* (14). Each question that is not answered correctly counts as one mistake (range of 0–10 mistakes). The cutoff point to establish a significant cognitive impairment is set at more than 2 mistakes, since in our cohort, older patients could read and write.

### ***Statistical analysis***

Frequency tabulation and summary statistics are listed to characterize the data distributions. Also, we studied if there were statistically significant differences in blood cell counts and, more specifically, in populations of lymphocyte counts between the older patients with a Pfeiffer result of 0–2 mistakes (not significantly impaired) *vs.* 3–10 mistakes (impaired). The Kolmogorov-Smirnov test was used for the distribution test. The non-parametric Mann-Whitney U test was used to assess differences in lymphocyte subpopulation counts between patients with a significantly diminished cognitive function and a normal cognitive status. Multiple regression models were used to assess the impact of clinical parameters on lymphocyte count. A difference with P value of less than 0.05 was considered to be statistically significant.

## **Results**

### ***Patients***

Seventy patients were analyzed in the study. The demographic characteristics of the patients, the tumor type, clinical stage and classification based on the result of the Pfeiffer test are summarized in *Table 2*. Patients ranged in age from 70 to 90 years. Median age was significantly higher in the group with cognitive impairment (80 *vs.* 76 years; P=0.0257), and this was considered in the subsequent multivariate analysis. In our cohort, 14.3% were female and most patients had a former or current history of a smoking habit (81.4%). The performance status was 0–1 in 75.8% of patients. Among all the patients analyzed, 85.7% [60/70] were considered to have a normal cognitive function, and 14.3% [10/70], an impaired cognitive status.

**Table 2** Demographics and clinical characteristics of older patients diagnosed with non-small cell lung cancer (NSCLC)

Variable	Patients (n=70)
Age (years), median [range]	77 [70–90]
Sex, n (%)	
Male	60 (85.7)
Female	10 (14.3)
Smoking status, n (%)	
Non-smoker	6 (8.6)
Current smoker	10 (14.3)
Ex-smoker	54 (77.1)
ECOG PS score, n (%)	
0	23 (32.9)
1	30 (42.9)
2	13 (18.6)
3	4 (5.7)
Histology, n (%)	
Adenocarcinoma	35 (50.0)
Squamous carcinoma	30 (42.9)
Other	5 (7.1)
Clinical stage, n (%)	
I	6 (8.7)
II	10 (14.5)
III	31 (44.9)
IV	22 (31.9)
Pfeiffer test, n (%)	
Normal (0–2 mistakes)	60 (85.7)
Significantly impaired (3–10 mistakes)	10 (14.3)

ECOG PS, Eastern Cooperative Oncology Group Performance Status.

Among patients with cognitive impairment, 80% were male [8/10].

In the general blood cell count, only lymphocyte count was significantly different between the two groups: patients with cognitive impairment had lower levels of lymphocytes (median lymphocyte count 1,200 *vs.* 1,500,  $P=0.0328$ , data shown in *Table 3* and *Figure 1*). *Table 3* also shows the median lymphocyte count and the interquartile range depending on the cognitive status of the patients included

in the analysis.

### *Relationship between NK lymphocytes and cognitive status*

Regarding the innate immunity, the median value of NK lymphocyte was similar between the two groups: in patients with a significantly impaired cognitive function the median value was 268 *vs.* 271 cells/mm<sup>3</sup> in the group of not impaired cognitive status ( $P=0.4513$ ).

### *Relationship between T lymphocytes and cognitive status*

Next, the subpopulation of T lymphocytes was analyzed: the median value of the total T-lymphocyte count was significantly lower in the group considered to have cognitive impairment, 882 cells/mm<sup>3</sup> (impaired) *vs.* 1,027 cells/mm<sup>3</sup> (not impaired) ( $P=0.0490$ ) (*Figure 1*). However, no differences were observed for the for CD4<sup>+</sup> T lymphocytes (504 *vs.* 556 cells/mm<sup>3</sup>,  $P=0.0948$ ) and for CD8<sup>+</sup> T lymphocytes (341 *vs.* 404 cells/mm<sup>3</sup>,  $P=0.1091$ ).

### *Relationship between B lymphocytes and cognitive status*

In the subset of B-lymphocyte population, the median value showed to be statistically lower in the cohort with impaired cognitive status (41 *vs.* 74 cells/mm<sup>3</sup>,  $P=0.0146$ ). Significant differences between cell-count levels according to cognitive status are also shown in *Figure 1*.

### *Multivariate analysis*

With these results, we performed the multivariate analysis using multiple regression models, taking into consideration, not only cognitive status, but also age, nutritional condition and tumoral stage. To assess nutritional status body mass index (BMI) and serum levels of albumin were considered. As shown in *Table 4*, cognitive status (not impaired *vs.* impaired) was an independent factor related to total lymphocyte levels, T-lymphocyte count and, specifically CD8<sup>+</sup> T lymphocytes. The coefficient obtained was negative in all three cases, showing that patients with an impaired cognitive function had significantly lower levels of these cell subsets. Interestingly, age was only positively correlated to the level of CD8<sup>+</sup> T lymphocytes (*Table 4*).

Subsequently, a multiple logistic regression analysis was performed, including age and the main lymphocyte subsets (B-lymphocytes, T-lymphocytes and NK-lymphocytes). The logistic regression analysis revealed

**Table 3** Median and interquartile range of cell count in peripheral blood samples from older patients based on their results of the SPMSQ

Parameters	Normal Pfeiffer test (n=60)	Altered Pfeiffer test (n=10)	P value
Hemoglobin (g/dL)	12.9 [11.9–14.4]	12.8 [12.3–13.8]	0.7096
Platelets ( $10^3$ cells/mm <sup>3</sup> )	232 [197–292]	228 [188–297]	0.5854
Neutrophils (cells/mm <sup>3</sup> )	5,650 [4,200–7,200]	5,850 [5,300–7,500]	0.4616
Lymphocytes (cells/mm <sup>3</sup> )	1,500 [1,100–2,300]	1,200 [600–1,400]	0.0328
NK-lymphocyte count (cells/mm <sup>3</sup> )	271 [204–461]	268 [94–347]	0.4513
T-lymphocyte count (CD3 <sup>+</sup> ) (cells/mm <sup>3</sup> )	1,027 [762–1,580]	882 [457–938]	0.0490
CD4 <sup>+</sup> T-lymphocyte count (cells/mm <sup>3</sup> )	556 [423–776]	504 [297–591]	0.0948
CD8 <sup>+</sup> T-lymphocyte count (cells/mm <sup>3</sup> )	404 [267–646]	341 [270–450]	0.1091
B-lymphocyte count (cells/mm <sup>3</sup> )	74 [53–115]	41 [17–67]	0.0146

SPMSQ, short portable mental status questionnaire; also, Pfeiffer test; NK, natural killer.

that age was significantly associated with a higher risk of cognitive impairment [odds ratio (OR) 1.1969 (95% CI: 1.022–1.400),  $P=0.0254$ ]; and higher levels of T-lymphocytes were associated with a lower risk of cognitive impairment [OR 0.996 (95% CI: 0.995–0.998),  $P=0.037$ ]. Levels of B-lymphocytes and NK-lymphocytes showed no significant association with cognitive impairment.

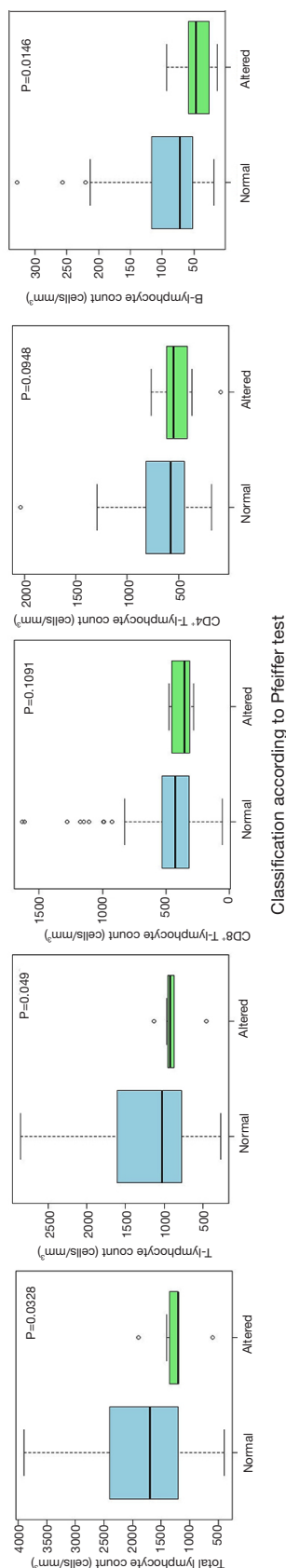
## Discussion

In this study we analyzed blood count parameters in patients older than 70 years diagnosed with NSCLC, who had been tested for cognitive dysfunction with the SPMSQ, and our results show that cognitive impairment is significantly associated with a lower lymphocyte count, and specifically reduced total and CD8<sup>+</sup> T-lymphocyte levels. To our knowledge, this is the first study that demonstrates a significant correlation between immunological status and cognitive function in patients with cancer.

It is known that cognitive impairment is more prevalent in aged individuals (15), and older age is also a risk factor for cancer development; and these are two of the conditions related to immunological shifts in the elderly. That is why, at this point, it is essential to outline the main changes that occur in the immune system during aging, in a process that is denominated immunosenescence. As described previously, immunosenescence is characterized by a reduced response capacity to new antigens and increased number of memory and senescent cells associated with low grade of chronic inflammation, known as inflammaging (8,9). This changes have been deeply investigated regarding the distribution of T cell subpopulations: in elderly healthy people, naïve

T-lymphocytes decrease (CD8<sup>+</sup>CD28<sup>+</sup>CD45RA<sup>+</sup>) and highly mature terminally differentiated cells increase (CD8<sup>+</sup>CD28<sup>-</sup>CD45RA<sup>+</sup>) (16,17). However, to study these subpopulations would imply using more specific antibodies that are not currently used in clinical practice and that surpass the objective of this investigation. Interestingly, results regarding total CD8<sup>+</sup> and CD4<sup>+</sup> lymphocytes have been conflicting in old healthy individuals, and higher and lower CD8<sup>+</sup> total lymphocyte counts have been reported in healthy older individuals (18,19). Moreover, changes in the B-lymphocyte population (CD19<sup>+</sup>) have been described, and a decrease in their total number has been observed. Also, NK lymphocytes have been examined with a high interest because of its part in tumour cell destruction. During normal aging, the function of these cells reduces, but this is balanced because the number of these cells increases (20). Although classically these changes were associated with a loss of functionality, their impact is still not completely understood and even to a lesser extent in patients with cancer.

Our findings support the results of the publication by Magaki *et al.* (21), including older patients with and without cognitive impairment. In this study, patients diagnosed with mild cognitive impairment had a significantly lower level of total lymphocytes and higher level of neutrophils. However, they were not able to find differences among lymphocyte subsets. The evidence of differential lymphocyte levels according to cognitive status, is also sustained by several studies that have correlated higher levels of neutrophil to lymphocyte ratio (NLR) to cognitive impairment (22,23). Although there is scarce data about specific lymphocyte subsets in patients with



**Figure 1** Absolute count of lymphocyte subsets quantified by flow cytometry in older patients diagnosed with NSCLC and divided into two groups based on their cognitive status defined by the result of the SPMSQ (univariate analysis). NSCLC, non-small cell lung cancer; SPMSQ, short portable mental status questionnaire.

cognitive impairment, there is increasing evidence of the relationship between inflammatory status and cognition (24,25). Mechanisms by which cognitive impairment is related to inflammatory status are not fully understood, nevertheless, systemic inflammation could induce a similar level of central nervous system inflammatory status mediated by different mechanisms, including activation of peripheral nerves (26) and increased permeabilization of the BBB, both inducing the production of proinflammatory cytokines by the microglia and astrocytes. Inflammation at this level would alter brain structures and could be associated with functional declining (27). Nonetheless, the connection between cognitive impairment and the level of T lymphocytes is harder to elucidate. Older patients in our study with cognitive impairment had significant lower levels of total, T and CD8<sup>+</sup> lymphocytes compared to elders with normal cognitive functioning, regardless of chronological age, which could indicate more extensive changes related to immunosenescence (17), or even sequestration of CD8<sup>+</sup> T-lymphocytes in the central nervous system as postulated by Richartz-Salzburger *et al.* (28) in a study including patients with Alzheimer disease with a similar lymphocyte distribution to the one reported in our analysis. Nevertheless, although a higher risk of cognitive impairment was also found in patients with lower levels of T-lymphocytes, due to the cross-sectional design of our study, no causal correlations could be established. On the other hand, in old healthy people, it has been observed that naïve T-lymphocytes decrease in number (mainly among the CD8<sup>+</sup> subpopulation) and highly mature terminally differentiated cells increase in number (16,29), including an increased number of autoreactive T lymphocytes that lead to higher levels of proinflammatory markers [such as IL-6 and C-reactive protein (CRP)] and participating in neural degeneration (30). That is why, lymphocyte distribution and differentiation and their correlation with cognitive impairment is being investigated including larger and prospective cohorts of patients diagnosed with lung cancer.

The rationale of exploring the relationship between immunological and cognitive status of patients diagnosed with lung cancer is considerable: firstly, during the last few years there has been a great development in Oncology of new drugs that work enhancing the immune system to fight against the tumor. This is especially interesting in advanced lung cancer, because it is known that it is a tumor with an important inflammatory component, and many immunotherapy agents used in the clinical practice are directed to this neoplasm (31,32). That is why it is

**Table 4** Multivariate analysis including clinical parameters that could be related to lymphocyte counts in older patients with lung cancer (age, Pfeiffer test result, BMI, albumin and tumoral stage)

Parameters	Coefficient for total lymphocytes (95% CI), P value	Coefficient for T lymphocytes (95% CI), P value	Coefficient for CD8 <sup>+</sup> T lymphocytes (95% CI), P value	Coefficient for CD4 <sup>+</sup> T lymphocytes (95% CI), P value	Coefficient for B lymphocytes (95% CI), P value
Age	16.47 (−19.84 to 52.79), 0.3678	20.52 (−4.98 to 46.03), 0.1127	17.87 (0.93 to 34.80), 0.0390	2.51 (12.78 to 17.81), 0.7435	−1.48 (−4.43 to 1.50), 0.3248
Pfeiffer test (normal vs. impaired)	−724.25 (−1,276.08 to −172.42), 0.0110	−507.55 (−896.05 to −11.06), 0.0113	−310.74 (−568.70 to −52.82), 0.0190	−210.84 (−443.86 to 22.17), 0.0753	−43.00 (−87.00 to 0.92), 0.0548
BMI (kg/m <sup>2</sup> )	−7.16 (−54.73 to 49.42), 0.7645	−2.91 (−35.24 to 30.40), 0.8616	−9.71 (−31.83 to 12.41), 0.3833	3.96 (−16.027 to 23.95), 0.6932	−2.25 (−6.02 to 1.42), 0.2386
Albumin (g/dL)	−128.55 (−657.67 to 400.58), 0.6287	−69.65 (−440.01 to 300.72), 0.7081	−86.30 (−332.19 to 159.58), 0.4853	11.91 (−210.24 to 234.05), 0.9150	−8.27 (−50.10 to 33.56), 0.6939
Tumoral stage (I to IV)	−120.26 (−345.69 to 106.17), 0.2922	−69.09 (−228.54 to 90.35), 0.3895	−0.58 (−106.43 to 105.28), 0.9913	−62.13 (−157.77 to 33.50), 0.1987	−10.86 (−28.94 to 7.22), 0.2344

BMI, body mass index.

essential to study the variations in the immune system in these patients and other clinical parameters that could influence immunological modulation during aging, such as cognitive impairment (21). Secondly, cancer-related cognitive impairment is a widely recognized entity, initially related to chemotherapy (33), radiation therapy and hormonal therapy (34), but that has proved to be present in patients before initiating any treatment and in patients after cancer surgery (35). The process by which cancer itself can induce cognitive impairment involves humoral responses, especially in lung cancer patients (36), and increased level of circulating proinflammatory cytokines related to lymphocyte repertoire (37). As all the patients included in our study had been diagnosed with NSCLC, we hypothesized that advanced tumoral stage might also influence immunological status, as reported in a study by Onyema *et al.* (38); however, we found no significant differences in lymphocyte populations depending on the extent of the disease. This differences could be due to the differences in the population included in their study, in which patients with small cell lung cancer and mesothelioma were also included, with a relatively low sample size (n=24 patients); but these disease's characteristics and evolution significantly differ from NSCLC and this could have acted as a confounding factor for the variation among lymphocyte subsets and should be investigated.

Moreover, besides aging, another crucial prognostic factor in lung cancer, that has also been related to immune modulation during aging is nutritional status (39-41).

Although BMI is a classical clinical parameter to evaluate nutritional condition, it has been demonstrated insufficient in patients diagnosed with cancer, as obese patients might also present with malnutrition (42,43), which is why, albumin was also included in multivariate analysis (44,45). Despite the data on previous publications, in our cohort, these nutritional parameters did not correlate to immunological status.

The limitations of our study include a relatively low sample size and its basis in a single center experience, which might have led to a lack of statistical power to detect differences in other lymphocyte subpopulations. Furthermore, not all the older patients diagnosed with NSCLC during the period of our analysis had been tested for their cognitive status until the comprehensive geriatric assessment was included in the diagnostic protocol of patients aged 70 years or more diagnosed with cancer in our Department, which explains the small size of the population analyzed. Also, although trends in lung cancer incidence have varied since the last few years, it is still a more prevalent disease in men (46); and consequently, there was a low percentage of female population eligible for our analysis. This, added to the relatively reduced sample size, is why potential gender differences could not be assessed. However, this fact is not considered a major issue because although Alzheimer disease is more prevalent in women, mild cognitive impairment incidence is similar in both sexes (47). Additionally, the most significant changes described in the immune system of older people are

mainly described in subsets of CD8<sup>+</sup> T lymphocytes that have different functionality (divided into naïve, central memory, effector memory and terminally differentiated effector memory cells using surface markers) (16). Although variations in the immune system could not only be related to aging, but also to clinical impairment, we did not perform these determinations, because this surpasses the scope of this study and warrants further exploration. On the other hand, one of the strengths of our study is that the only major exclusion criteria are suffering from an autoimmune or a chronic infectious disease, resulting in a highly heterogeneous sample that is similar to the patients we encounter in clinical practice. Furthermore, despite the reduced number of patients diagnosed with cognitive impairment, statistically differences were found, and these results make our investigation a relevant hypothesis generating study. Finally, the use of a widely extended technique as flow cytometry, which is available in most hospitals, allows for applying these determinations in routine clinical practice.

Taken together, our results suggest that immune changes in older patients diagnosed with NSCLC are connected not only to age, but also to clinical parameters. The comprehensive geriatric assessment is a widely recognized tool to evaluate older patients with cancer and encompasses many different areas of human functioning. It has been proved that chronological age is not sufficient to characterize the heterogeneity of the older people diagnosed with cancer (48) and it is crucial to identify a subset of patients that can have reduced life expectancy and possibly a different expected benefit and toxicity of new treatments such as immunotherapy. That is why it is of particular interest to further study the possible relationship between the immunological status and functional, environmental or cognitive situation. Specifically, understanding risk factors for cognitive dysfunction and the interaction between cancer treatment and the aging process would help oncologists to weigh the potential benefits and risks of therapy, and guide treatment decision making.

In conclusion, immunosenescence is a widely recognized phenomenon in general population, mainly related to aging. Nonetheless, the impact of functional, cognitive, or nutritional status especially in oncologic patients has not been deeply assessed yet. Our data show that cognitive impairment is related to a lower count of lymphocytes, and specifically of T-lymphocyte and CD8<sup>+</sup> subsets. These findings suggest that clinical parameters are closely correlated to immunological status in older patients

diagnosed with NSCLC. However, this needs further investigation, and this is why we are performing studies regarding clinical parameters of geriatric assessment including larger cohorts and deeper analysis of lymphocyte differentiation.

### Highlights

- (I) Immunosenescence refers to the changes that occur in the immune system during aging;
- (II) Cognitive dysfunction is associated with changes in immune system in cancer patients;
- (III) Low T-cell count is seen in cancer patients with cognitive impairment besides age;
- (IV) Age cannot always explain immunosenescence, geriatric assessment could help.

### Acknowledgments

The authors would like to express our gratitude to Joanna Gołab for her contribution preparing the manuscript.

*Funding:* None.

### Footnote

*Reporting Checklist:* The authors have completed the STROBE reporting checklist. Available at <http://dx.doi.org/10.21037/tcr-20-1997>

*Data Sharing Statement:* Available at <http://dx.doi.org/10.21037/tcr-20-1997>

*Peer Review File:* Available at <http://dx.doi.org/10.21037/tcr-20-1997>

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr-20-1997>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and it was approved by the Ethics Committee of the Hospital Universitario Doctor Peset (ID local code 77/17). Written informed consent was exempted



because of the retrospective nature of the study and assured anonymity.

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**Cite this article as:** Soria-Comes T, Palomar-Abril V, Martín Ureste M, García Sánchez J, Marco Buades JE, Fernández Llavador MJ, López Gabaldón A, González Jurado M, Maestu Maiques IC. Cognitive impairment is related to a reduced count of T-lymphocytes in older patients diagnosed with non-small cell lung cancer (NSCLC). *Transl Cancer Res* 2020;9(11):6857-6866. doi: 10.21037/tcr-20-1997