Correlation between the prevalence of T-cell lymphomas and alcohol consumption

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DOI: 10.15386/mpr-1777

Manuscript received: 13.06.2020
Received in revised form: 27.11.2020
Accepted: 29.03.2021

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Abstract

Background and aims. Alcohol is a psychoactive substance that causes dependence, with many thousands of years in the history of mankind, being widely used in different cultures. According to the International Agency for Research on Cancer, alcohol is involved in the development of cancer, being directly associated with it. Considering that alcohol is involved in the initiation and dissemination of gastrointestinal malignancies, the objective of the study was to assess its role in the pathogenesis of T-cell lymphomas, as well as its possible correlation with chronic consumption.

Methods. The patient cohort was compiled from the Sixth Medical Center of the People's Liberation Army Navy General Hospital in Beijing, China. A total of 30 patients matched the criteria and were enrolled in the study. Statistical analysis of the raw data was performed using R Statistics version R 3.5.1. released on the 29.08.2018.

Results. Our data demonstrate that the most common extranodal involvment of T-cell lymphoma patients is represented in decreasing order by bone marrow, peritoneum, rhino-oropharynx and the liver-biliary system. Nodal involvement is mainly represented in decreasing order by the laterocervical, axillary, mediastinal and inguinal regions.

Conclusions. These findings may be of value in further research and practical/clinical settings. Fever is the most common clinical feature and was present in most studied patients.

Keywords: T-cell lymphomas, alcohol consumption, pathophysiology

Introduction

Over the past century the incidence of non-Hodgkin lymphomas (NHL) has steadily risen, mainly the B-cell lymphomas, as they represent the majority of NHL [1–3]. T-cell and NK-cell lymphomas are generally underrepresented due to their low incidence overall. They also have a wide variability in different geographical regions and racial populations [4–6]. T- and NK-cell lymphomas are relatively rare and clinically either of these subtypes are aggressive and quite heterogenous [7]. The occurrence of adult T-cell lymphomas may be linked to previous viral infections with Human T-lymphotropic virus type 1 (HTLV-1) and Epstein-Barr virus (EBV) [8–14]. Considering that T-cell lymphomas in general, are a rarely occurring type of malignancy, its large number of subtypes represent only a few hundred cases annually.

While in North America the three most commen T-cell lymphomas are peripheral T-cell lymphoma - Not Otherwise Specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma and anaplastic large-cell lymphoma ALK-positive (ALCL ALK-positive), Europe

shows a relatively equal distribution with one exception: anaplastic large-cell lymphoma ALK-negative (ALCL ALK-negative) replaces ALCL ALK-positive of North America. In Asia, the prevalence of the three most common T-cell lymphomas is quite different, with a nearly equal distribution of PTCL-NOS, NK/T-cell lymphomas, and adult T-cell leukemia / lymphoma (ATLL). The latter two are up to twenty-five times more frequent in Asia than in North America or Europe [15–18].

Alcohol is a psychoactive substance with certain dependence producing properties and a long history of many thousands of years in human history and was widely used in different cultures [19]. Many factors have an impact on the total or individual consumption of alcoholic beverages, for example sociodemographic factors, economic development, religion, culture as well as individual factors such as gender, age, health status, personal economic wealth, and lifestyle [20–23]. To measure the level of alcohol consumption some indicators need to be defined and explained. The most important are the prevalence/number of current drinkers and abstainers in a region or country, as well as the total alcohol consumption in liters of pure alcohol per person per year and the alcohol consumption in grams of pure alcohol per person per day [24–27]. According to the WHO data from 2016 the total aclohol per capita consumption in the world population of age 15 years and older was on average 6.4 liters of pure alcohol annually which accounts for 13.9 grams of pure alcohol per day [28,29]. Elimination of alcohol mainly occurs in the liver by the alcohol dehydrogenase and cytochrome P450 oxidation of ethanol, a small percentage, below 1% is eliminated by breath, urine and sweat [30,31].

Alcohol dehydrogenase (ADH) is found in different organs throughout the body; it is found in the highest amounts in the liver, followed by GI tract, kidneys, nasal mucosa, testes, and in the uterus, it is located in the cytosolic fraction of the cell. It has a variety of oxidative functions and is involved in the steroid and bile acid metabolism. It oxidizes endogenous alcohol produced by microorganisms in the gut and exogenous ethanol and other alcohols consumed in the diet [32].

Racial groups express different amounts of the ADH1, which could explain a variation in the metabolism of alcohol. The International Agency for Research on Cancer (IARC) has classified acetaldehyde as a type 1 carcinogen in humans [33,34].

Alcohol metabolism and the resulting metabolites lead to an increase in the risk of the development of certain cancers associated with the consumption of alcohol [35]. The World Health Organization (WHO) has identified chronic alcohol consumption as one of the top ten risk factors in terms of the years of life lost to premature mortality and years lived with disability. The most serious adverse health factors resulting from chronic alcohol consumption may be the development of cancer [36–38].

Taking into consideration that alcohol is involved in cancer initiation and dissemination, the objective of this research is devoted to T-cell lymphomas and its possible correlation with the chronic consumption of alcohol. Thus, we currently present the results of a pilot epidemiology study carried out as a result of a collaborative study between Romania and China.

Methods

Patient cohort

The patient cohort was compiled from the Sixth Medical Center of People's Liberation Army Navy General Hospital in Beijing, China, under the coordination of Dr. Liren Qian. The gathering of the data was conducted using patient charts from recent years with histologically confirmed and diagnosed T-cell lymphomas of all subtypes. Patients of any age, sex, geographical region, co-morbidities, risk factors and ethical background were included in this study. Inclusion in this study was not possible if data concerning the usage of alcohol in the past or present were not available. This led to the exclusion of the patient from the studied cohort. A total of 30 patients matched these criteria and were enrolled in the study. Data from the patient charts were translated in a pre-assembled Excel-Sheet with previously chosen important demographical and clinical characteristics with regard to the studied objective to give a precise overview of the patient and the accompanied pathology related features. A subdivision of the Excel-Sheet into three divisions for organizational purposes was conducted to assure a quick overview of the collected data.

Statistical analysis

Statistical analysis of the raw data was performed using R Statistics version R 3.5.1. released on the 29.08.2018.

Results

Patient demographics of the 30 enrolled patients is presented in table I (Demographical characteristics), table II (Extranodal sides) and table III (Nodal sides). The percentage of drinkers according to the histological subtypes of T-cell lymphomas is depicted in figure 1. The p-value (p=0.370) is not statistically significant, but this might be because of the small sample. "Drinkers" seem to present more frequently with angioimmunoblastic T-cell lymphoma (AITL), while "Never drinkers" seem to present more frequently with Adult T-cell Leukemia/Lymphoma (ATLL). If comparing AITL versus non-AITL the p-value is 0.0753 (a total of 38 patients would be needed to observe if there is statistical significance or not). If comparing ATLL versus non-ATLL the p-value is 0.632. This brings the hypothesis that alcohol consumption might be a risk factor for developing AITL and should be tested on a larger cohort.

Table I. Demographical characteristics.

Demographic characteristics	Value	Value
Sex	Male	26
	Female	4
Mean age (sd)		49.93 (20.55)
Area	Urban	17
	Rural	13
Fever	No	10
	Under 38	2
	Over 38	18
Weight loss	No	16
	Under 10%	10
	Over 10%	4
Night sweats	No	23
	Yes	7
ECOG	0	0
	1	21
	2	8
	3	1
	4	0
Erythroderma	No	25
	Yes	5
Raised rush	No	24
	Yes	6
Pruritis	No	25
	Yes	5
Fatigue	No	19
	Yes	11
Headache	No	29
	Yes	1
Neurologic symptoms	No	29
	Yes	1
Cough	No	27
	Yes	3
Dyspnea	No	28
	Yes	2
Anorexia	No	18
	Yes	12
Abdominal pain	No	25
	Yes	5

Table II. Extranodal sites.

Extranodal sites	Value
CNS	1
Eye and lacrimal glands	0
Rhino-Oro-Pharynx	8
Salivary gland	0
Thyroid	1
Parotid	0
Heart	0
Vascular system	3
Pericardium	2
Thymus	1
Lungs	1
Pleura	0
Liver and biliary system	7
Pancreas	0
Colon and rectum	2
Kidneys	1
Peritoneum	10
Genital system	2
Spleen	5
Bone	3
Skin	2
Subcutaneous	2
Muscle	1
Breast	1
Bone marrow	11

CNS - Central Nervous System

Table III. Nodal sites.

Nodal sites	Value
Waldeyer's ring	1
Submandibular	3
Laterocervical	21
Axillary	17
Lung hilum	6
Mediastinum	16
Celiac	2
Lomboaortic	3
Mesenteric	1
Iliac	7
Inguinal	14
Crural	1

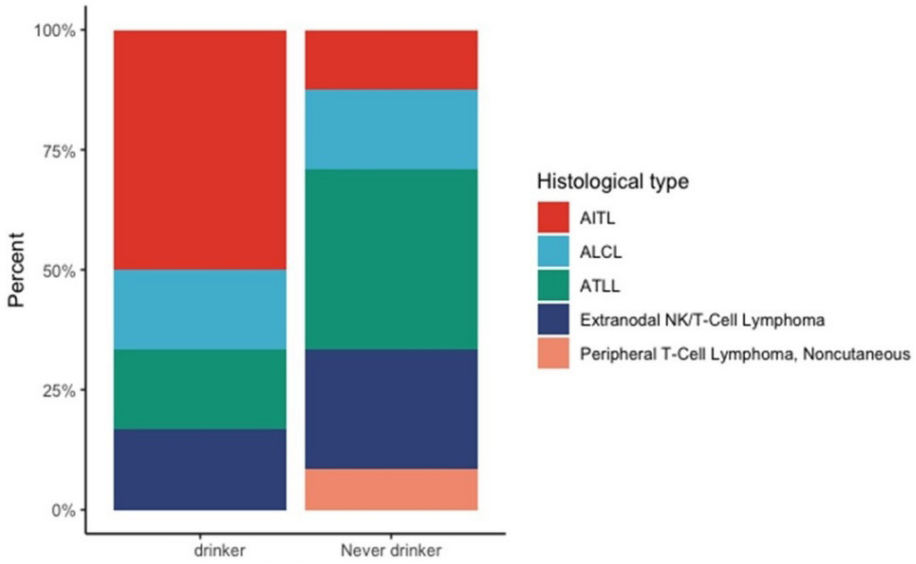

Figure 1. Percentage of drinkers according to the T-cell lymphoma subtypes. AITL- angioimmunoblastic T-cell lymphoma; ALCL - anaplastic large cell lymphoma; ATLL - adult T-cell leukemia/lymphoma.

The drinking behavior according to the extranodal site involvement is depicted in figure 2, while the drinking behavior according to the nodal side involvement is depicted in figure 3. Because of the small number of drinkers and former drinkers per extranodal site, it is not possible to draw a valid statistical conclusion and this graph is only descriptive. The most frequent four sites have similar distributions of drinkers. Other nodal sites do not have enough observations that would make them important.

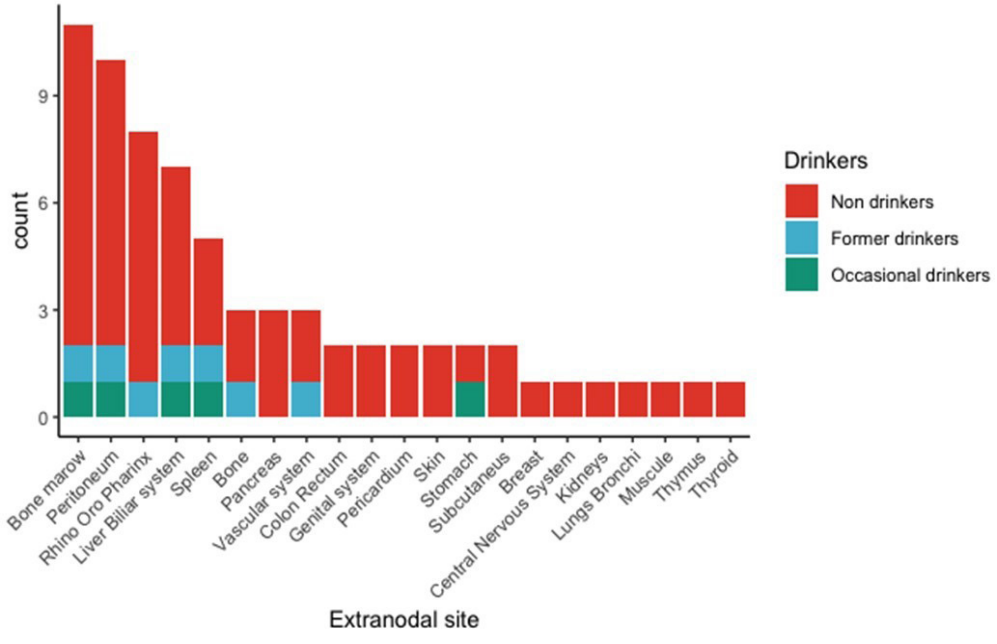

Figure 2. Drinking behavior according to the extranodal site involvement.

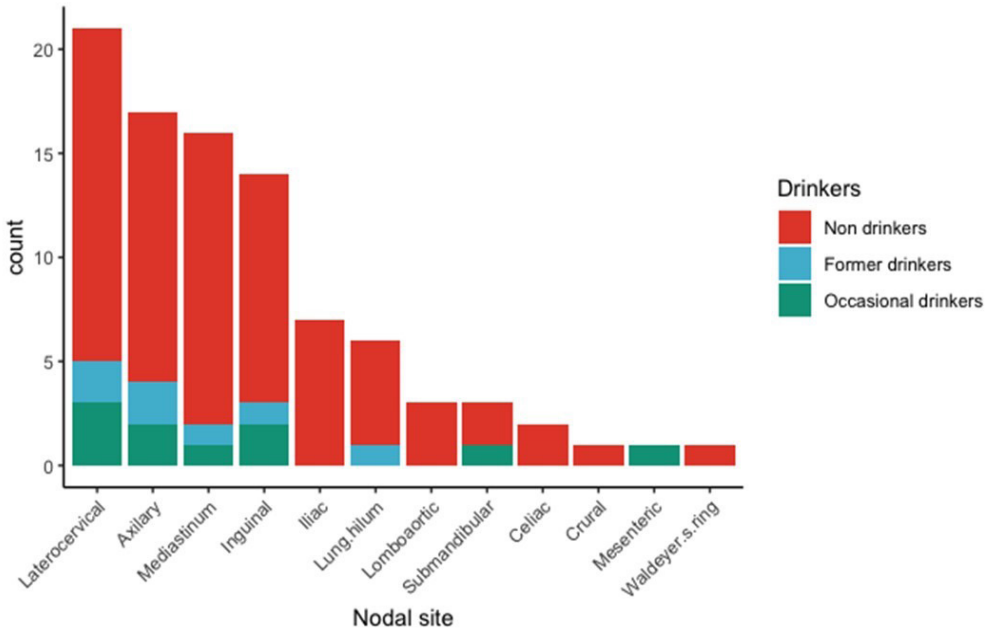

Figure 3. Drinking behavior according to the nodal site involvement.

The correlation between drinking behavior and clinical symptoms is shown in figure 4. Fever was close to statistical significance (p=0.0741), but all 6 alcohol consumers had fever and 20 out of 30 patients had fever. There might have been a result regarding fever if a larger cohort would have been considered. Statistical analysis includes p = 0.0605 for rural urban, p = 0.00256 for smoking and p = 0.0843 for education. Smoking should also be considered when expanding the cohort, as it will act as a confounding variable. Education and rural/urban areas, although they did not reach the cutoff of 0.05, should be observed as they might reach statistical significance in a larger cohort and act as confounders.

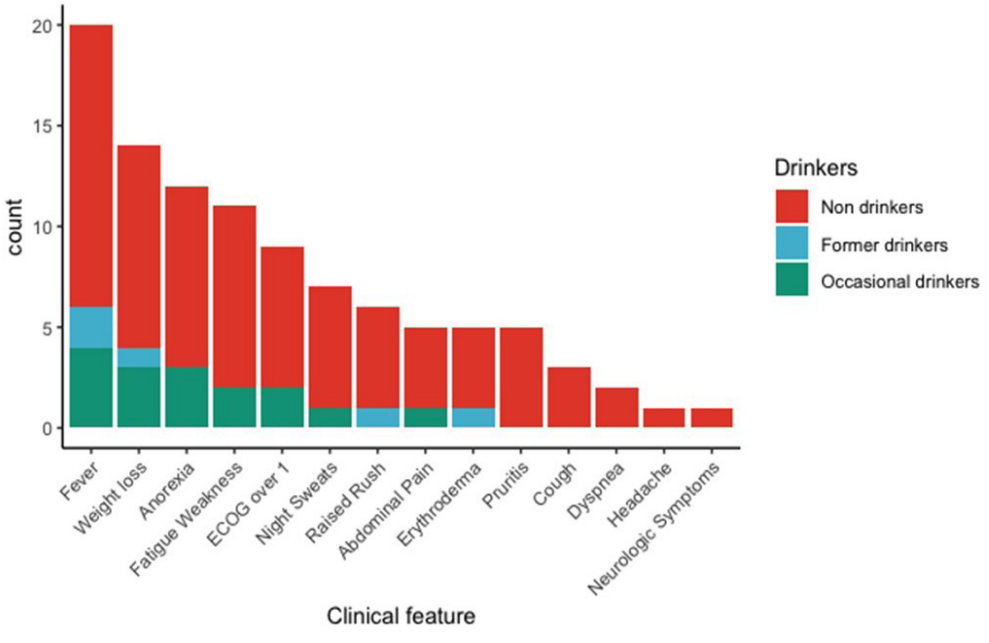

Figure 4. Correlation between drinking behavior and symptoms.

Discussion

Commercially produced alcoholic beverages belong to the most consumed source of alcohol in developed countries worldwide. They include mainly beer produced from barley, wine produced from grapes and different types of distilled beverages [39]. Alcohol/Ethanol content can vary heavily between the different kinds of beverages. The WHO defines as current drinkers the percentage of those in the population aged 15 years and older who have consumed alcoholic beverages in the previous 12-month period. Total alcohol per capita consumption (APC) is defined as the total (recorded plus estimated unrecorded) alcohol per capita (i.e. persons aged 15 years and older) consumption within a calendar year in liters of pure alcohol, adjusted for tourist consumption. This indicator is used for the total population of 15 years and older (including non-drinkers) and for current drinkers only in the population [40].

The countries of the WHO European Region top the list of the highest per capita consumption of alcohol worldwide with 10 liters or more annually. In a few exceptions a relatively equal consumption is observed in countries from the WHO Africa Region e.g. Nigeria, from the WHO Region of the Americas e.g. Uruguay or in Australia and New Zealand. Also, a high consumption of 7.5-9.9 liters of pure alcohol per capita is found in the WHO Regions of Americas and the Western Pacific Region with a high income but also in some countries of the African Region. The lowest per capita consumption of less than 2.5 liters in found in the WHO Eastern Mediterranean Region and in Muslim-majority countries such as Niger in WHO African Region, Indonesia in the WHO South-East Asia Region (SEAR), or Azerbaijan in the WHO European Region [29].

According to the International Agency for Research on Cancer (IARC), alcohol as a carcinogen, is involved in the development and directly associated with cancer of the oral cavity, pharynx, larynx, esophagus, liver, colorectum, and the female breast. Approximately 389,000 of these cancers and thus 3.6% of its total occurrence are related directly with chronic alcohol consumption [41]. Since 2010 alcohol was classified as type 1 carcinogen by the International Agency for Research on Cancer (IARC), today both alcohol and the acetaldehyde metabolite are classified as type 1 carcinogens. The development of cancer was proven to follow a J-shaped risk profile where the risk increases dramatically with a higher amount of exposure to risk factors of any kind. When we translate this finding to the consumption of alcohol, it is shown that when drinking below a certain threshold namely “moderate drinking” the risk of developing cancer is equal or less compared to non-drinkers and would increase dramatically with the amount of alcohol ingested [42].

Previous studies have shown that the consumption of alcohol may be associated with a reduced risk of NHL [43,44]. This finding may mirror the fact that the vast majority of 80% of our T-cell lymphoma patient are non-drinkers while only 6 out of the 30 patients were either former drinkers or are current drinkers. It was also presented that wine drinkers had an overall better survival compared to non-drinkers with NHL: the opposite was the case with the consumption of liquor. To transfer these findings to our cohort, a long-term follow-up is necessary as well as the assessment of the type of consumed alcohol to make precise differentiations. It is important to mention that the consumption of liquor goes along with a lower socio-economic status which could be on its own a risk factor for the development of malignancies. The opposite is valid for the consumption of wine. Additionally, it was shown that wine does not only have a positive influence on the survival of NHL patients but also prevents its relapse and the development of secondary cancers. This phenomenon may be scientifically supported by the theory that the polyphenolic constituents in grapes such as flavonoids and resveratrol, block the carcinogenesis by its anti-oxidative and anti-inflammatory properties. Contrary to these propositions other studies have shown that the consumption of alcohol is correlated with a poorer outcome of NHL patients in terms of survival and the increased risk of death. These findings confirm our hypothesis of a correlation between alcohol consumption and T-cell lymphoma development. This study also states that cigarette smoking is associated with a poorer overall survival in NHL [45]. This aspect would be of value to take into consideration in the follow up of our cohort; 25 out of 30 patients, 83.33% of our cohort have never smoked and thus reached statistical significance ($p = 0.00256$).

This finding raises the hypothesis of smoking as a protective factor for T-cell lymphoma and should be taken into account to establish a correlation between smoking and T-cell lymphoma development when conducting a larger scale cohort in future research. In a future study with a larger cohort it would be also worthwhile to establish a certain threshold or cut-off value for alcohol consumption and the proportional increase in the risk to develop lymphomas. This could validate the assumption that a J-shaped risk curve is also applicable in the correlation between alcohol and T-cell lymphomas. Unfortunately, we cannot make a noteworthy statement regarding this hypothesis because just 6 out of 30 (20%) patients were either drinkers or former drinkers with three consuming between 1-149 g/week and only one over 300g/week of alcohol.

Our data demonstrate that the most common extranodal involvement of T-cell lymphoma patients is represented in decreasing order by bone marrow, the peritoneum, rhino-oropharynx and the liver-biliary system. Nodal involvement in mainly represented in decreasing order by the laterocervical, axillary, mediastinal and inguinal regions. These findings may be of value in further

research and practical/clinical settings. Fever is the most common clinical feature and was present in 20 out of 30 (66.67%) studied patients. Attention should also be directed to the area of living as rural/urban (p=0.0605) came close to statistically significant; the same can be applied for educational status (p=0.0843).

Educational status is often linked with a higher or lower socioeconomic status. Our cohort had an equal distribution of educational status with 26.67% without education, 26.67% university, 23.33% gymnasium and 23.33% high school education. Due to this we cannot draw a conclusion if T-cell lymphoma development is associated with the socioeconomic status. The majority of studies are not conclusive if a low socioeconomic status is generally correlated with a higher risk of cancer development as the data vary depending on the type of cancer. One study states that a lower socioeconomic status is related with a late stage diagnosis of malignancies and consequently with poorer survival.

These factors deserve special attention when conducting a larger cohort in the future and may give an important insight regarding correlations to T-cell lymphoma development.

The major limitations of the study are in relation to the data collection, exact anamnesis and history of the patients is of crucial importance and should be documented precisely. Unfortunately, not enough attention was given to the alcohol exposure history of the patient which made it difficult to include patients in this study and which lead consequently to this relatively small cohort. To obtain precise statements with regard to volume frequency and history of alcohol consumption by the patients is another limiting factor as statements often are not reliable or precise enough to benefit from those. This is especially true in establishing a threshold in grams of alcohol consumed and the associated increasing risk for the development of malignancies. Also, the fact that T-cell lymphomas represent a minority of cancers, few cases are available in a geographically limited surrounding such as a single hospital or department. These limitations made it difficult to gather sufficient data to make statistically significant statements and to support our hypothesis. But the potential of the study was proven and gives a valuable cornerstone and starting point for further research in this area.

Unfortunately, this study did not have enough power to draw conclusions regarding the constructed hypothesis. The main reason is the limited number of patients in our cohort. Nevertheless, the study design has the potential to draw valid conclusions regarding correlations between risk factors and malignancy occurrence. A similar setup with a larger cohort is advisable for further research; a differentiation between the type of alcohol consumed, the volume, time period and drinking habits must be considered.

Conclusion

Although the understanding of NHL and T-cell lymphomas has improved over the years, further research on this pathology is necessary focusing on the many unanswered questions.

Large scale epidemiological studies need to be established to gain valuable insights into the development of T-cell lymphomas. Small studies such as ours may give the impetus for larger resource settings. The main conclusion from our cohort is that there is still no clear answer whether alcohol is a protective or risk factor.

Nevertheless we established the hypothesis that alcohol consumption might be a risk factor for developing AITL and should be tested in a larger cohort. 88.33% of our cohort never smoked cigarettes which raises the hypothesis of smoking as a protective factor for T-cell lymphoma. These findings should be put in focus when conducting further research.

Acknowledgements

Minodora Desmirean and Cedric Richlitzki contributed equally to the current paper and are both considered first author. Minodora Desmirean was financed from an internal grant of the School of Doctoral Studies - Iuliu Hatieganu University (PCD 2018-2021). Ciprian Tomuleasa was also supported by two national research grants of the Romanian Government: the first one awarded for Frontiers Research Projects 2018-2022 (grant number PN-III-P4-ID-PCCF-2016-112), awarded to the Babes Bolyai University in collaboration with the Ion Chiricuta Oncology Institute Cluj Napoca. Also a second one, awarded for Young Research Teams 2020-2022 (grant number PN-III-P1-1.1-TE-2019-0271) awarded to the Iuliu Hatieganu University of Medicine and Pharmacy Cluj Napoca. Ciprian Tomuleasa, Bobe Petrushev and Delia Dima were also financed by an international collaborative grant of the European Economic Space between Romania and Iceland 2020-2022 (grant number 19-COP-0031).

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