RESEARCH ARTICLE

The Influence of GPX1 Pro198Leu, CAT C262T and MnSOD Ala16Val Gene Polymorphisms on Susceptibility for Non-Hodgkin Lymphoma and Overall Survival Rate at Five Years from Diagnosis

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Objective: The aim of the current study was to investigate possible associations between catalase C262T (*CAT* C262T), glutathione peroxidase 1 Pro198Leu (*GPX1* Pro198Leu), manganese superoxide dismutase Ala16Val (*MnSOD* Ala16Val) gene polymorphisms and non-Hodgkin Lymphoma risk (NHL) in a Romanian population and the five-year overall survival rate of the NHL patients. **Methods**: We included in this case-control study 406 individuals, divided into two groups: the control group (n=315) and the patients group (n=91). The DNA was extracted from peripheral blood and amplified using specific techniques. **Results**: The variant homozygous genotype of *GPX1* Pro198Leu represents a risk factor for NHL development and no associations regarding the risk for NHL were found for *MnSOD* Ala16Val and *CAT* C262T gene polymorphisms. Two of the studied polymorphisms were associated with the overall survival rate thus: negative association regarding *MnSOD* Ala16Val, associated with higher overall survival rate and a positive one regarding *CAT* C262T, associated with lower overall survival rate. **Conclusions**: According to our results, the mentioned polymorphisms may be considered as susceptible markers of the five-year overall survival rate for NHL patients. Future studies with a larger number of patients are needed to confirm our results.

Keywords: NHL, GPX1, CAT, MnSOD polymorphism

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Introduction

Non-Hodgkin Lymphoma (NHL) is a heterogeneous type of blood cancer characterized, like all malignancies, by an abnormal cellular proliferation [1]. NHL represents the most common type of lymphomas (90%) and may be classified into two groups, mature B-cell neoplasms and mature T-cell and natural killer (NK)-cell neoplasms [1,2]. One study conducted by Perry et al. demonstrated that the frequency of NHL subtypes is significantly different in some geographical regions. Also, the median age of patients with low-grade and high-grade of NHL in North America is significantly higher than in the Far East [3]. These findings suggest that differences between some etiological aspects and host risk factors are likely responsible, but for a better understanding of these differences, more epidemiological studies are needed [3,4].

In Romania or Eastern and Central Europe, only a few studies are being involved in analyzing new risk factors for NHL and even fewer studies are addressing the role and the risk of different genetic variants [5,6]. The distribution of NHL subtypes in South-eastern Europe reported by Dotlic et al. in 2015 was: 91.1% of B-cell lymphomas and 8.9% of NK-cell lymphomas [7].

Chronic inflammation is a major risk factor which was reported to be connected to NHL, although the mecha-nism underlying this connection is still ambiguous [8]. An aspect that could sustain this matter is the fact that neoplasia is known to be in some cases induced by oxidative stress caused by inflammation, which can generate reactive oxygen species (ROS) that lead to oxidative DNA damage [9]. In addition, ROS propagate pro-inflammatory cytokines, including interleukin-1 which stimulates B cells to produce antibodies that trigger a signal for B-cell activation [10].

Furthermore, a number of studies highlighted that several diseases such as arthritis, systemic lupus erythematosus, and Sjögren's syndrome, characterized all by a chronic B-cell activated phenotype, have been associated with an increased risk of developing NHL [11,12,13].

ROS can also be inactivated by anti-oxidant enzymes such as catalase (*CAT*), glutathione peroxidase (*GPX*) and manganese superoxide dismutase (*MnSOD*) which protect the cells from the negative effects of oxidative stress [10,14].

According to SNPedia [15] and NCBI [16], there is a consistent number of single nucleotide polymorphisms (SNPs) of the human catalase gene. In the last few years, there has been a significant number of case-control and meta-analysis studies [17,18] focusing on the *CAT* C262T polymorphism (substitution of Cytosine with Thymine in the 262 position of the promotor) involved in the progression of neoplasia, but more studies regarding NHL are still needed [10,19].

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GPX1 is an additional antioxidant enzyme involved in the cell protection mechanisms against the ROS effects, reducing lipid hydroperoxides to their corresponding alcohols and free hydrogen peroxide to water. A specific polymorphism caused by the substitution of Proline (Pro) with Leucine (Leu) at position 198 (*GPX1* Pro198Leu, rs1050450), has previously been reported to be associated with decreased enzyme activity and increased risk for developing cancer [20].

Manganese superoxide dismutase (*MnSOD*), another antioxidant enzyme, protects the cells against oxidative stress. The superoxide radicals are eliminated after their conversion to water and oxygen [18]. *MnSOD* Ala16Val is one of the few polymorphisms previously investigated in NHL patients [10, 21] and correlated with enzyme activity and cancer risk [18, 20, 22].

To the best of our knowledge, none of the published studies have evaluated *CAT*, *GPX1* and *MnSOD* gene polymorphisms in patients with NHL in Central or Eastern Europe.

The aim of the current study was to investigate possible associations between *CAT* C262T, *GPX1* Pro198Leu, *MnSOD* Ala16Val gene polymorphisms and NHL risk in a Romanian population and their influence on the overall survival rate of NHL diagnosed patients.

Method
Patients and Controls
We conducted a population based case-control study, which consisted of 406 individuals from the same geographical area with a similar ethnical background (central region of Romania), divided into two groups: the control and the patients group. The patients group consisted of 91 adults with a confirmed diagnosis of NHL, admitted to the Hematology Clinics, of Emergency Clinical County Hospital of Târgu Mureș, Romania, between 2010 and 2016. Our control group included 315 healthy participants with no hematological malignancies and no history of cancer or other chronic diseases.

The approval of the present study was obtained from the Ethics Committee of the University of Medicine and Pharmacy of Târgu Mureș and was conducted according to the principles of the Declaration of Helsinki.

Clinical and histological diagnosis of NHL has been made according to the WHO standards [2], with the following distribution of NHL subtypes: 35 patients with Diffuse large B-cell lymphoma (DLBCL), 16 patients with Follicular lymphoma (FL), 16 patients with Marginal zone B-cell lymphoma (MBZL), 10 patients with Primary Non-Hodgkin Lymphoma (Pl), 7 with T-Cell Lymphoma, 2 with Mucosa-associated lymphoid tissue lymphomas (MALT), and 5 other types.

Clinical and laboratory data, such as histopathological classification of the NHL, the Eastern Cooperative Oncology Group Scale of Performance Status (ECOG), International Prognostic Index (IPI), Ann Arbor stage, treatment response, five-year survival rate, Lactate dehydrogenase (LDH) levels and extranodal sites were collected and analyzed from the patients' medical records.

Genotyping Procedures
Two milliliters of fresh peripheral blood were collected from patients and controls, at the time of their routine blood collection, in sterile tubes with Ethylenediaminetetraacetic acid (EDTA), for DNA extraction. DNA was isolated using the Quick-gDNA MiniPrep kits (ZymoResearch, USA) and Wizard Genomic DNA Purification kits (Promega, Madison, WI, USA) according to the manufacturer´s instructions.

The DNA absorbance was verified by spectrophotometric quantification (BioSpectometer, Eppendorf, Germany). In order to analyze the genotypes of the mentioned SNPs, RFLP-PCR technique was performed using specific primers and FastDigest restriction enzymes, as previously reported [18, 23, 24].

Statistical Analysis
Data analysis was performed using GraphPad InStat software, MedCalc. Chi-square test and Fisher's exact test in order to compare the distribution of qualitative variables between cases and controls. Associations between genotypes, combined variant genotypes (homozygous and heterozygous), allele distribution among NHL patients and control groups were calculated as odds ratios (OR), recommended in case-control studies, with 95% confidence intervals (CI) and a significance level of 0.05.

Results
The distribution of allele's frequency and genotypes of the *CAT* C262T, *GPX1* Pro198Leu, and *MnSOD* Ala16Val among NHL patients and controls are shown in Table I.

No significant association was found between the presence of variant alleles of *CAT* C262T and *MnSOD* Ala-16Val SNPs and NHL risk, but the variant homozygous genotype of *GPX1* Pro198Leu represents a risk factor for NHL development (*p* value = 0.04).

Although the number of cases analyzed is relatively low, we have studied the combined variant genotypes. The results for the combined *CAT* C262T, *GPX1* Pro198Leu and *MnSOD* Ala16Val genotypes and alleles among NHL patients and controls, are presented in Table II. In this case, no significant differences were observed between the presences of variant genotypes or variant alleles for all three investigated SNPs and NHL risk.

Furthermore, we evaluated the effect of these SNPs in detail, taking into account different risk factors such as gender, age, histological subtype of the lymphoma, survival rate, treatment response, LDH levels, and extranodal sites. Table III summarizes the clinical characteristics of NHL patients according to the genotypes. No differences were found regarding elevated LDH levels and variant genotypes/ alleles for the investigated SNPs (*p* value>0.05).

Table I. Distribution of CAT C262T, GPX1 Pro198Leu and MnSOD Ala16Val genotypes and alleles among NHL patients and controls

	NHL Patients	Controls	p value	OR	95%CI
CAT C262T					
CC	54	165	Reference		
CT	32	130	0.26	0.75	0.45-1.23
TT	5	20	0.80	0.76	0.27-2.13
CC+CT	37	150	0.28	0.75	0.46-1.21
Allele					
C	140	460	Reference		
T	42	170	0.33	0.81	0.55-1.19
GPX1 Pro198Leu					
Pro/Pro	2	26	Reference		
Pro/Leu	59	205	0.08	3.74	0.86-16.23
Leu/Leu	30	84	0.04	4.64	1.03-20.76
Pro/Leu+Leu/Leu	89	289	0.05	4.00	0.93-17.20
Allele					
Pro	63	257	Reference		
Leu	119	373	0.14	1.30	0.92-1.83
MnSOD Ala16Val					
Ala/Ala	7	33	Reference		
Ala/Val	64	208	0.54	1.45	0.61-3.43
Val/Val	20	74	0.81	1.27	0.49-3.3
Ala/Val+Val/Val	84	282	0.55	1.4	0.59-3.29
Allele					
Ala	78	274	Reference		
Val	104	356	0.93	1.02	0.73-1.43

Table II. Distribution of combined CAT C262T, GPX1 Pro198Leu and MnSOD Ala16Val genotypes and alleles among NHL patients and controls

	NHL Patients	Controls	p value	OR	95%CI
Combined genotypes					
CC+Pro/Pro+Ala/Ala	1	5	Reference		
CT+Pro/Leu+Ala/Val	12	83	0.57	0.72	0.07-6.73
TT+Leu/Leu+Val/Val	1	1	0.46	5	0.14-166.73
CT or TT+ Pro/Leu or Leu/Leu+ Ala/Val or Val/Val	37	128	1	1.44	0.16-12.76
Combined alleles					
C+Pro+Ala	12	68	Reference		
T+Leu+Val	14	58	0.52	1.36	0.586-3.191

In addition, we investigated the impact of these SNPs by the clinical manifestations such as Ann Arbor stage, ECOG or IPI. No associations were found between the presumed risk groups and variant genotypes of CAT C262T, GPX1 Pro198Leu, and MnSOD Ala16Val gene polymorphisms (Table III).

Regarding the influence of allele's and genotypes in treatment response, no differences were noticed between NHL patients outcome and the investigated SNPs (p value >0.05) (Table III).

Moreover, we performed a comparison between different variant (heterozygous and homozygous) genotypes of CAT C262T, GPX1 Pro198Leu, and MnSOD Ala16Val, and the survival rate of our patients. We found that two of the studied polymorphisms were associated with the survival rate thus: negative association regarding MnSOD Ala16Val, associated with a higher survival rate (p value = 0.031, OR = 0.15, CI 95% 0.028-0.078) and a positive association regarding CAT C262T, associated with a lower survival rate (p value = 0.025, OR = 3.763, CI 95% 1.208-11.721). The results for both heterozygous genotypes of MnSOD and CAT are statistically significant. While analyzing in detail, by allele frequency, both MnSOD 16Ala variant allele (p value = 0.33, OR = 0.73, CI95% 0.4-1.3) and CAT 262C variant allele (p value = 0.27, OR = 1.435, CI 95% 0.76-2.67) showed no association. The study was based on a relatively low number of carriers of the variant homozygous genotype, a fact that may have led to a non-statistically significant results in those cases. However, according to combined variant genotypes (heterozygous and homozygous- Dominant model), the results remained statistically significant, but only for CAT C262T polymorphism.

Life expectancy of NHL cases according to the genotypes is graphically represented in Figure 1. The five year overall survival rate is calculated and described with Kaplan Meier curves, and is estimated to be: CAT C262T (p value = 0.017) CC – 80%, CT – 43%, TT – 100%, GPX1 Pro198Leu (p value = 0.704) Leu/Leu - 82%, Pro/Leu – 60%, Pro/Pro – 100%, MnSOD Ala16Val (p value < 0.0001) Ala/Ala 43% Val/Ala 70%, Val/Val 75%.

No differences were found regarding clinical and demographical characteristics of patients and CAT, GPX1 and MnSOD variant genotypes (p value >0.05) (Table III).

Discussions

Important advances in the understanding of the molecular pathogenesis of malignant lymphomas have been made in the last few years. Several unforeseen compounds referring to the oncogenic signaling courses are studied in different trials in patients diagnosed with lymphoma [25]. The evidence towards the oxidative stress involvement as an important contributor to cancer, producing inflammation and DNA damage, is still standing [22].

Diminished MnSOD activity has been proved to be found in lymphoma tumors, as its increased activity induces apoptosis and suppresses tumorigenesis [22]. Furthermore, it has been showed that MnSOD2 Ala16Val, GPX1 Pro198Leu, and CAT C262T SNPs decrease the enzymatic activity, and by inducing DNA damage, they also produce a high risk for developing cancer [26,27].

In the present study, we investigated the CAT C262T, GPX1 Pro198Leu and MnSOD2 Ala16Val SNPs on NHL patients in order to evaluate the associations between the mentioned SNPs and NHL risk, clinical characteristics, treatment response and overall survival rate in a Romanian population, from the country's central region.

The CAT C262T polymorphism has been intensively studied because the allelic T variant is associated with a decreased enzyme activity [28], resulting in a high level of ROS which maintains the possibility of developing some types of cancer.

In a recent meta-analysis [17] of several studies regarding different cancer types, including hematological ones, it

Table III. Patients characteristics according to the CAT, GPX1 and MnSOD genotypes

Genotype / p value	CAT C262T					GPX1 Pro198Leu					MnSOD Ala16Val				
	CC	CT	p	TT	p	Pro/Pro	Pro/Leu	p	Leu/Leu	p	Ala/Ala	Ala/Val	p	Val/Val	p
No. patients	54	32		5		2	59		30		7	64		20	
Sex (men/women)	22/32	13/19	p>0.5*	2/3	p>0.5*	2/0	26/33	p>0.5*	9/21	p>0.5*	5/2	23/41	p>0.5*	9/11	p>0.5*
Age, median	58	68	p>0.5*	63	p>0.5*	59.5	58	p>0.5*	66.5	p>0.5*	70	60.5	p>0.5*	52	p>0.5*
Ann Arbor Stage															
Ann Arbor Stage 1,2 number of patients (%)	32(59.25)	18(56.25)	Ref.	2(40.00)	Ref.	1(50.00)	32(54.23)	Ref.	19(63.33)	Ref.	2(28.57)	38(59.37)	Ref.	12(60.00)	Ref.
Ann Arbor Stage 3,4 number of patients (%)	22(40.74)	14(43.75)	0.82	3(60.00)	1	1(50.00)	27(45.76)	1	11(36.66)	1	5(71.42)	26(40.62)	0.22	8(40.00)	0.208
LDH															
LDH < 280 UI number of patients (%)	26(48.14)	15(46.83)	Ref.	2(40.00)	Ref.	1(50.00)	26(44.06)	Ref.	16(53.33)	Ref.	5(71.42)	30(46.87)	Ref.	8(40.00)	Ref.
LDH > 280 UI number of patients (%)	28(51.85)	17(53.12)	1	3(60.00)	1	1(50)	33(55.93)	1	14(46.66)	1	2(28.57)	34(53.12)	0.26	12(60.00)	0.208
ECOG															
1,2 number of patients (%)	38(70.37)	21(65.62)	Ref.	2(40.00)	Ref.	1(50.00)	40(67.79)	Ref.	20(66.66)	Ref.	3(42.85)	44(68.75)	Ref.	14(70.00)	Ref.
3,4 number of patients (%)	16(29.62)	11(34.37)	0.81	3(60.00)	0.315	1(50.00)	19(32.20)	1	10(33.33)	1	4(57.14)	20(31.25)	0.216	6(30.00)	0.364
IPI															
0,1,2 number of patients (%)	26(48.14)	18(56.25)	Ref.	3(60.00)	Ref.	1(50.00)	31(52.54)	Ref.	15(50.00)	Ref.	2(28.57)	34(53.12)	Ref.	11(55.00)	Ref.
3,4,5 number of patients (%)	28(51.85)	14(43.75)	0.509	2(40.00)	0.670	1(50.00)	28(47.45)	1	15(50.00)	1	5(71.42)	30(46.87)	0.260	9(45.00)	0.384
Treatment response															
Resistant number of patients (%)	18(39.13)	18(58.06)	0.215	3(60.00)	0.532	1(50.00)	25(47.16)	1	13(48.14)	1	3(60.00)	31(51.66)	0.550	5(29.41)	1
Partial remission number of patients (%)	18(39.13)	9(29.03)	1	2(40.00)	0.540	1(50.00)	20(37.73)	1	8(29.62)	1	2(40.00)	16(26.66)	0.496	11(64.70)	1
Complete remission number of patients (%)	10(21.73)	4(12.90)	Ref.	0(0.00)	Ref.	0(0.00)	8(15.09)	Ref.	6(22.22)	Ref.	0(0.00)	13(21.66)	Ref.	1(5.88)	Ref.
Overall survival															
Survival number of patients (%)	39(86.66)	19(63.33)	Ref.	5(100.00)	Ref.	1(50.00)	40(75.47)	Ref.	22(84.61)	Ref.	3(42.85)	45(83.33)	Ref.	15(78.94)	Ref.
Death number of patients (%)	6(13.33)	11(36.66)	0.025	0(0.00)	1	1(50.00)	13(24.52)	1	4(15.38)	1	4(57.14)	9(16.66)	0.031	4(21.05)	0.149

*calculated for both, men and women; LDH- Lactate dehydrogenase; ECOG- the Eastern Cooperative Oncology Group Scale of Performance Status; IPI- International Prognostic Index
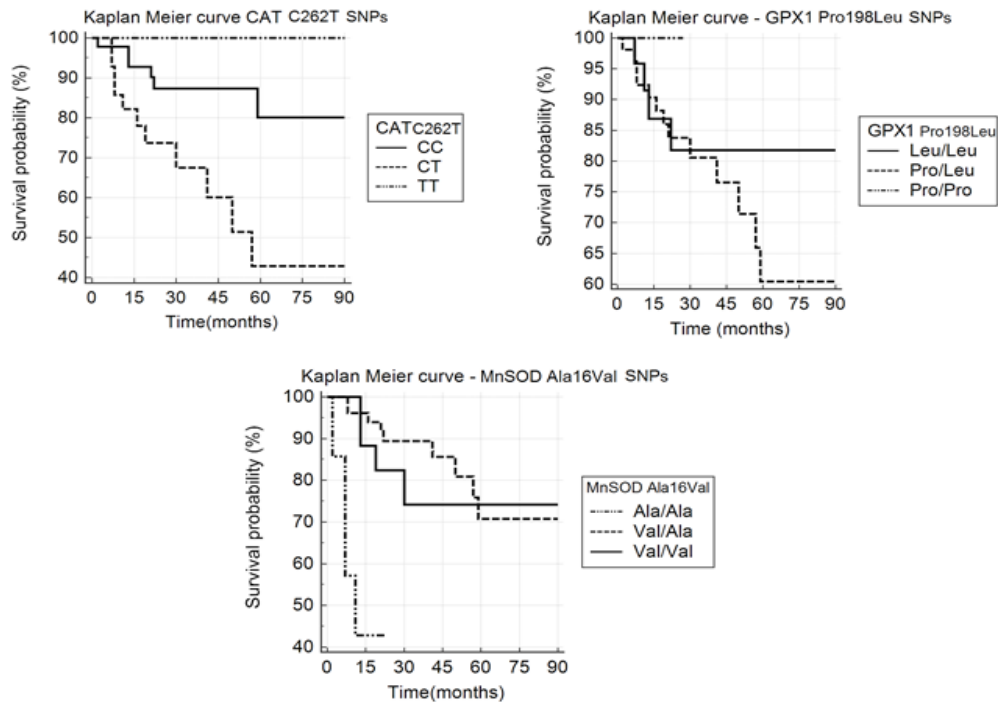
Fig. 1. Kaplan Meier survival curves of NHL patients according to the investigated CAT, GPX1 and MnSOD **gene polymorphisms**

was suggested that the *CAT* C262T polymorphism may be associated with cancer susceptibility, and even more, may be considered a potential tumor biomarker. Nevertheless, the *CAT* C262T polymorphism is not considered an accurate prognostic factor for cancer survival rate [17].

According to our results, the *CAT* C262T is not a risk factor for NHL development, but it was associated with lower overall survival rate in dominant model. However, the results should be interpreted with caution, due to the relatively small number of patients.

Additionally, well designed, multicenter studies are required in order to investigate the role of this functional polymorphism, which should lead to a better and more comprehensive interpretation of the associations between the *CAT* C262T polymorphism and NHL risk and the overall survival rate, preferable on a wider population.

Paz-y-Mino et al. revealed in their study that the association of *GPX1* Pro198Leu variant genotype with a decreased enzyme activity results in an increased risk of developing cancer in Caucasians [22]. Glutathione peroxidase has established its significant role as an antioxidant enzyme catalyzing the detoxification of hydrogen peroxide and being one of the most important enzymes discovered in humans [29].

In our study, we found an association between the variant homozygous genotype of *GPX1* Pro198Leu and the susceptibility for NHL, the mentioned SNP being a risk factor for NHL developing. We found no statistically significant differences between clinical parameters, treatment response or survival rate and the *GPX1* Pro198Leu polymorphism.

We found no differences in the distribution of the genotypes and alleles of *MnSOD2* Val16Ala among the two groups, but we highlighted a negative association of the het-erozygous genotype and the survival rate, suggesting that the presence of this genotype may represent a protective factor, being associated with higher overall survival rate.

To our current knowledge, nowadays there is still no evidence supporting the role of these SNPs referring to the clinical characteristics as well as the five-year overall survival rate in the same treatment conditions and counting out other causes of death. Contrary to our findings, there are studies describing a significant association between *MnSOD* Val6Ala polymorphism and the risk of developing DLB-NHL [21]. A meta-analysis performed by Kang et al. [30], showed an association between the *MnSOD* Val16Ala and the NHL susceptibility and other types of cancer. In the current study, we discovered no association referring to this gene polymorphism and NHL subtypes (*p* value >0.05).

We found a similarity between the results of our analysis and a pooled analysis that investigated 2293 NHL cases and 3432 controls (from UK and USA) which found no association of this variant with the overall risk of developing NHL, but an association of the variant homozygous genotype with a decreased MZL risk was uncovered [10].

Superoxide dismutase has still an unclear role as its deficient activity has been highlighted in malignant lymphomas [31]. In some animal-based studies, it has been proved that a reduced *MnSOD* activity leads to DNA damage and increased cancer incidence [32]. For that manner, further studies are needed in order to clarify the role of this gene.

The limitations of our study include the relatively small cohort of lymphoma patients and its retrospective design. The described impact of two additional polymorphisms in the manganese superoxidase dismutase and catalase gene on the overall survival in lymphoma is limited by the heterogeneous group of lymphoma diagnoses. Another limita-

tion is represented by the lack of enzymatic level of cata-
lase, glutathione peroxidase, superoxide dismutase.

Conclusions

In conclusion, the present study provides an evidence that
the *GPX1* Pro198Leu gene polymorphism might be a risk
factor for NHL in a Romanian population and that there is
a possible association between *CAT* C262T gene polymor-
phism and a low five-year overall survival rate in NHL pa-
tients. Furthermore, *CAT* C262T and *MnSOD* Val16Ala
gene polymorphisms appear not to be risk factors for the
development of NHL.

Authors' contribution

Adriana Stela Cosma (Conceptualization; Methodology;
Project administration)

Cristina Radu, Alexandra Moldovan (Data curation)

Alina Bogliş (Formal analysis)

George Andrei Crauciuc (Formal analysis)

Emőke Horváth (Data curation; Formal analysis; Valida-
tion)

Marcela Cândea (Data curation; Formal analysis; Valida-
tion)

Florin Tripon (Conceptualization; Funding acquisition;
Methodology; Resources; Supervision; Validation; Writing
– review & editing)

Acknowledgement

Conflict of Interest

The authors declare no conflict of interest.

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