A COMPARATIVE ANALYSIS OF THE SPANISH AND LATIN-AMERICAN PROSPECTIVE DRUG-INDUCED LIVER INJURY (DILI) NETWORKS

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INTRODUCTION

DILI characteristics concerning phenotype and involved drugs or other toxic compounds can vary between individuals and possibly between different geographic populations. We aimed to compare all DILI cases included in the ongoing Spanish and Latin-American DILI Network that share the same inclusion criteria and operational procedures.

MATERIAL & METHODS

Demographics, clinical parameters and causative agents were compared between 200 Latin-American and 867 Spanish DILI cases (Figure 1).

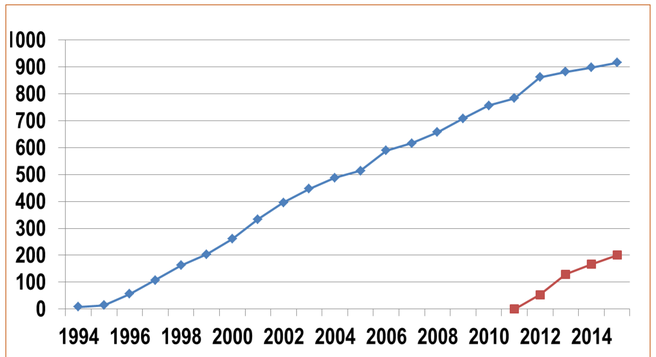

Figure 1. Case enrolments in the Spanish DILI Registry (◆) and SLATINDILI Network (■)

Table 2. Main drugs in both the Spanish and LatinAmerican Registries

Drug	Spanish DILI Registry	SLATINDILI Network
Amoxicillin-clavulanate	186	20
RIF+INH+PIR	29	7
Ibuprofen	22	7
Diclofenac	16	13
Isoniazid	22	4
Nimesulide	9	11
Stanozolol	12	7
Nitrofurantoin	2	11
Cyproterone	3	9

RESULTS

Table 1. Demographics and clinical characteristics between the Spanish DILI Registry and SLATINDILI Network

	Spanish DILI Registry N=867	SLATIN DILI Network N=200	p value
Age, mean (range)	54 (11-90)	51 (15-89)	**0.02**
Female sex, n (%)	422 (49)	117 (59)	**0.01**
Duration of treatment, mean (range) median	88 (1-2425) 27	127 (3-3724) 35	**<0.001**
Time to onset , median (range) median	80 (0-2425) 24	116 (0-3724) 31	**0.03**
Clinical presentation, n(%)			
Jaundice	583 (68)	132 (67)	0.8
Rash	59 (8)	24 (12)	**0.03**
Positive autoantibodies	156 (23)	53 (30)	**0.04**
Hospitalization	456 (59)	92 (46)	**0.001**
Severity, n(%)			**0.6**
Mild+moderate	742 (88)	170 (86)	
Severe	63 (8)	18 (9)	
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FHF-OLT	20 (2)	5 (2.5)	0.9
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Time to resolution, mean (range)	130	65	**<0.001**

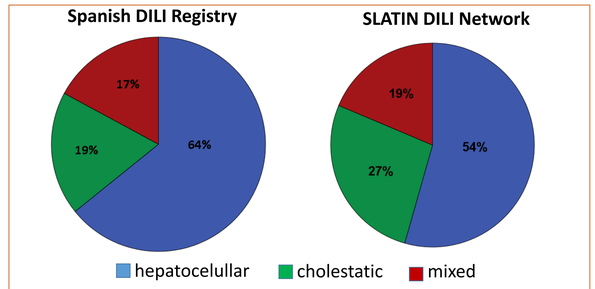

Figure 3. Type of liver injury in spanish vs latinamerican cases

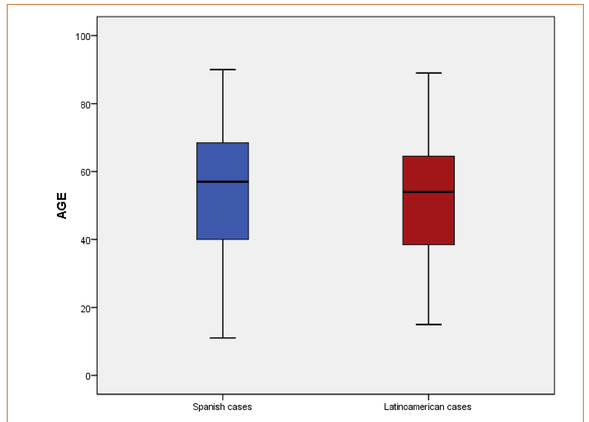

Figure 2. Distribution by age in spanish vs latinamerican cases

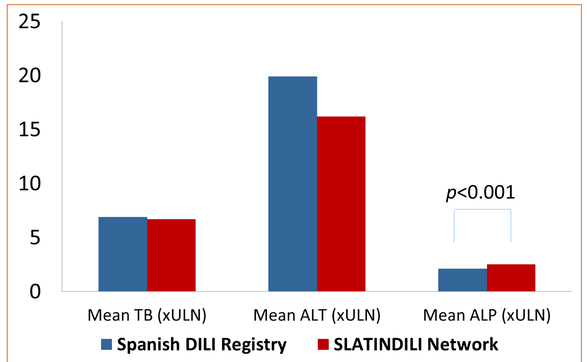

Figure 4. Laboratory parameters at onset in spanish vs latinamerican cases

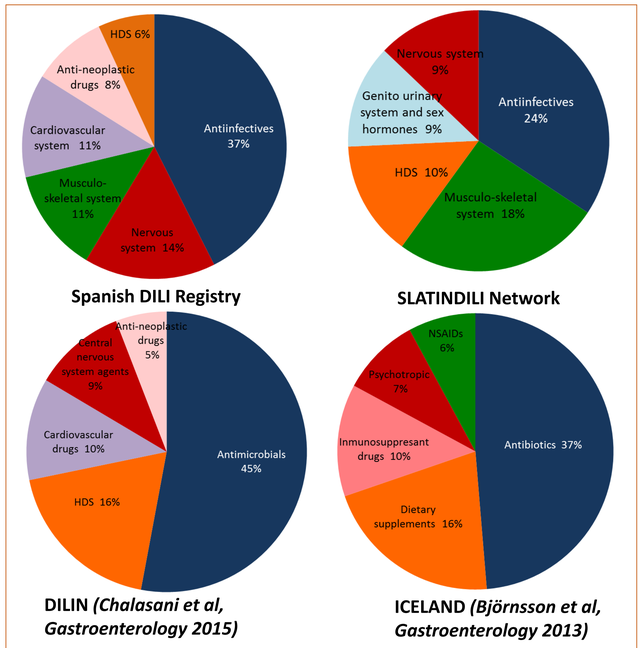

Figure 5. Most frequent drug classes in prospective DILI registries

The mean age of DILI development differed between the two registries with 51 years in LatinAmerica and 54 years in Spain (p=0.02) (Table 1, Figure 2). Females predominated among the LatinAmerican cases (59%) compared to the Spanish cases (49%) (p=0.01). Duration of treatment and time to onset were higher in LatinAmerican cases (127 vs 88 days, p <0.001) and (116 vs 80 days, p=0.03), respectively. Jaundice was similar (67% and 68%) between registries. Although hepatocellular damage was the most frequent type of injury in both registries (Figure 3), the percentage of hepatocellular cases was significantly higher in the Spanish Registry (63% vs 54%, p=0.03) and the mean alkaline phosphatase value at onset was higher in the Latin American cases (2.5 vs 2.1, p<0.001) (Figure 4). Severe cases (9% vs 8%) and fatal cases (liver-related death or liver transplantation) (4.6% vs 4%) did not differ. Antiinfectives ranked first in both registries, followed by nervous system and musculo-skeletal drugs in the Spanish DILI Registry (Figure 5). Musculo-skeletal and sex hormones predominated in the LatinAmerican cohort. Amoxicillin-clavulanate, diclofenac, nimesulide, and nitrofurantoin were the most common causatives in LatinAmerica, and amoxicillin-clavulanate, antituberculosis treatments, ibuprofen and atorvastatin in Spain (Table 2). Herbal and dietary supplements for bodybuilding DILI were more represented in LatinAmerica (10% vs 6%, p=0.05).

CONCLUSION

Phenotypic differences were found between the Latin-American and Spanish registries, with female and cholestatic/mixed type of liver injury predominating in the former cohort. In addition to genetic factors, variations in drug policies and prescription habits may account for the differences in causative agents, which, in turn, may present distinct DILI 'signatures' and explain the phenotypic variations.

Funding: Instituto de Salud Carlos III co-founded by Fondo Europeo de Desarrollo Regional – FEDER (contract numbers: PI12-00620, AC-0073-2013) and by the Agencia Española del Medicamento. CIBERehd is funded by Instituto de Salud Carlos III.

DISCLOSURES

Fernando Bessone - Advisory Committees or Review Panels: Schering Plough, Gilead, Glaxo, MSD, Janssen; Speaking and Teaching: Bristol Myers Squibb, Janssen, Bayer, Gilead, Abbvie. Miguel E. Garassini - Advisory Committees or Review Panels: Abbvie; Speaking and Teaching: Roche, Stendal.

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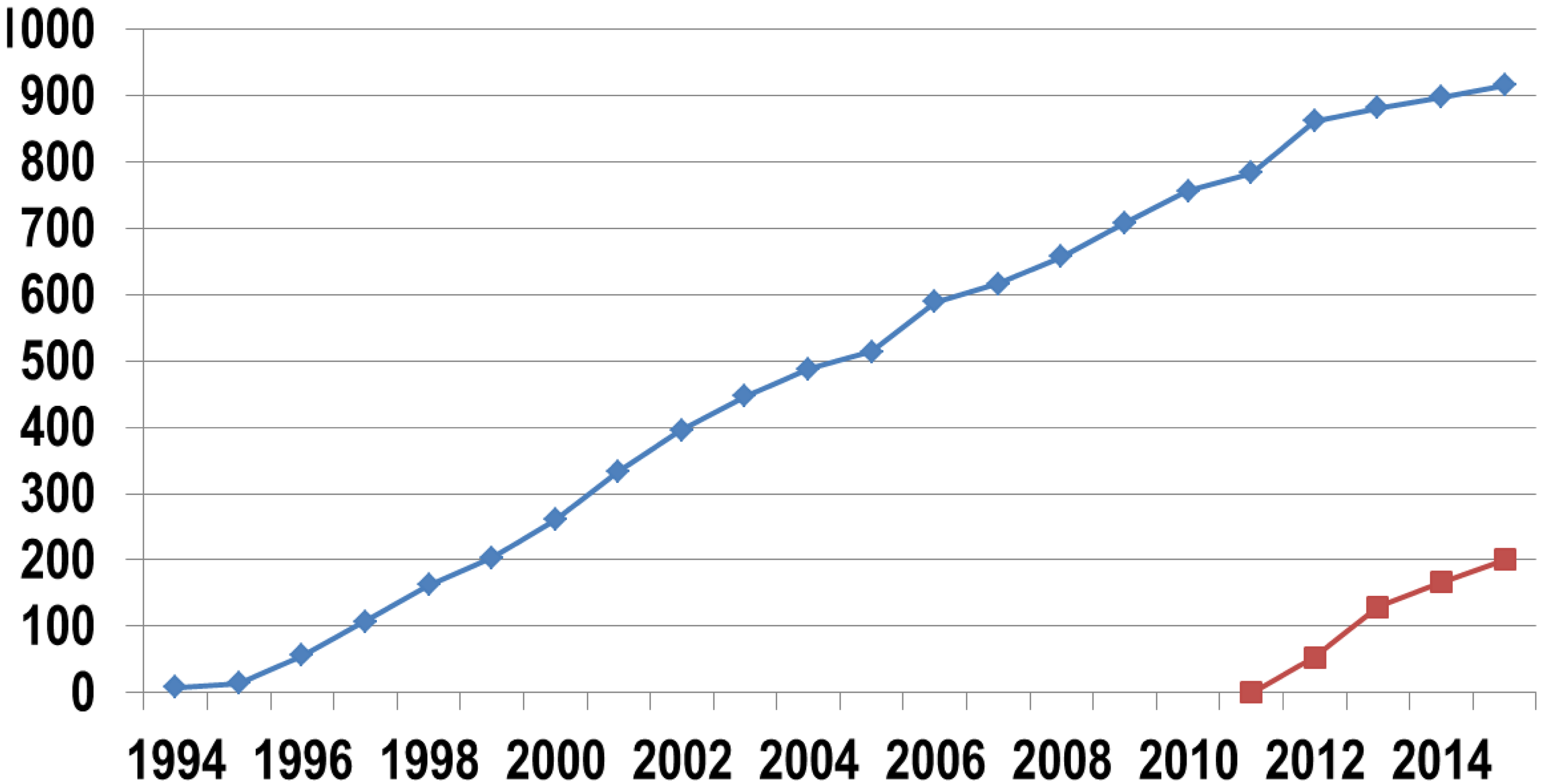

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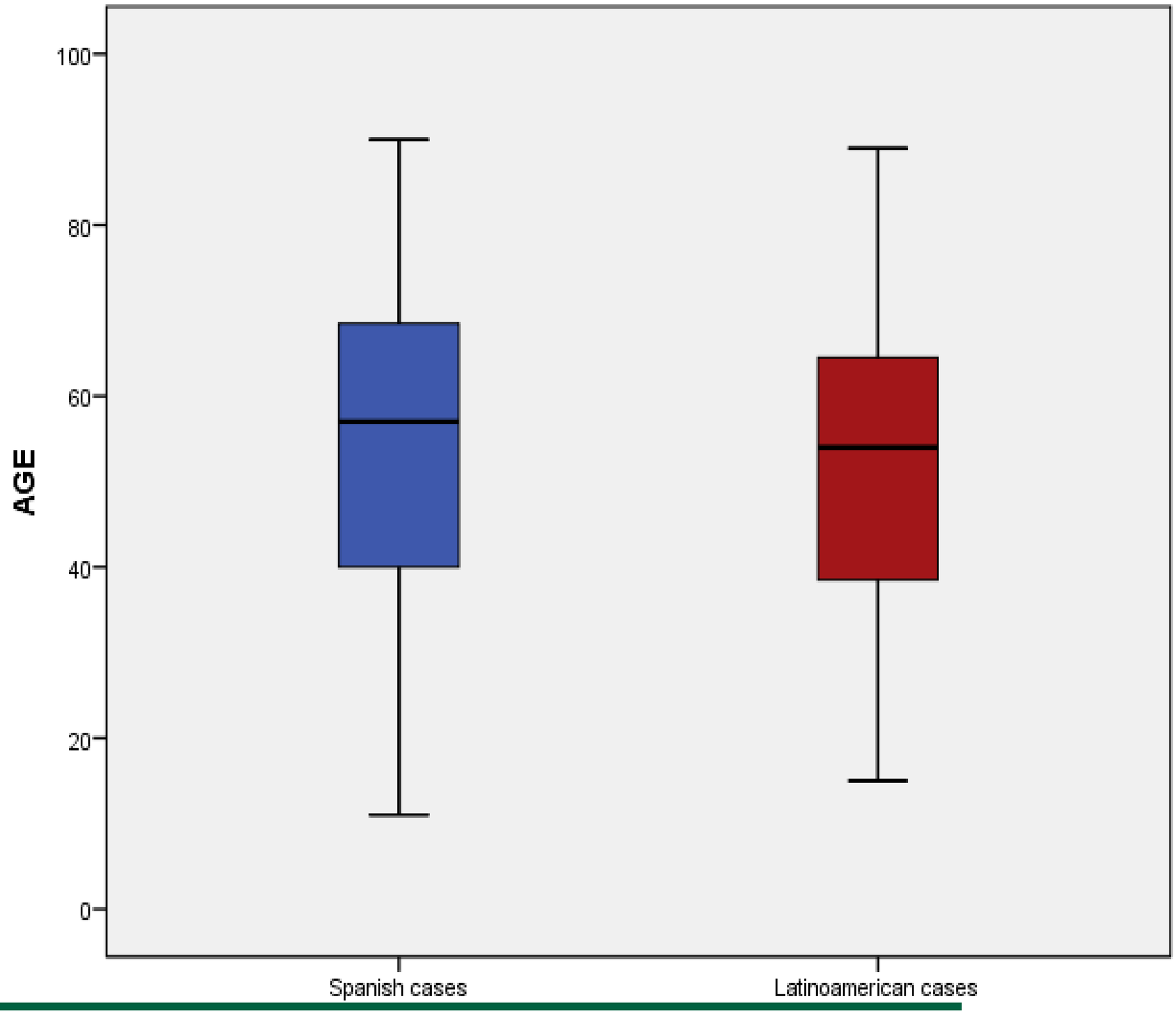

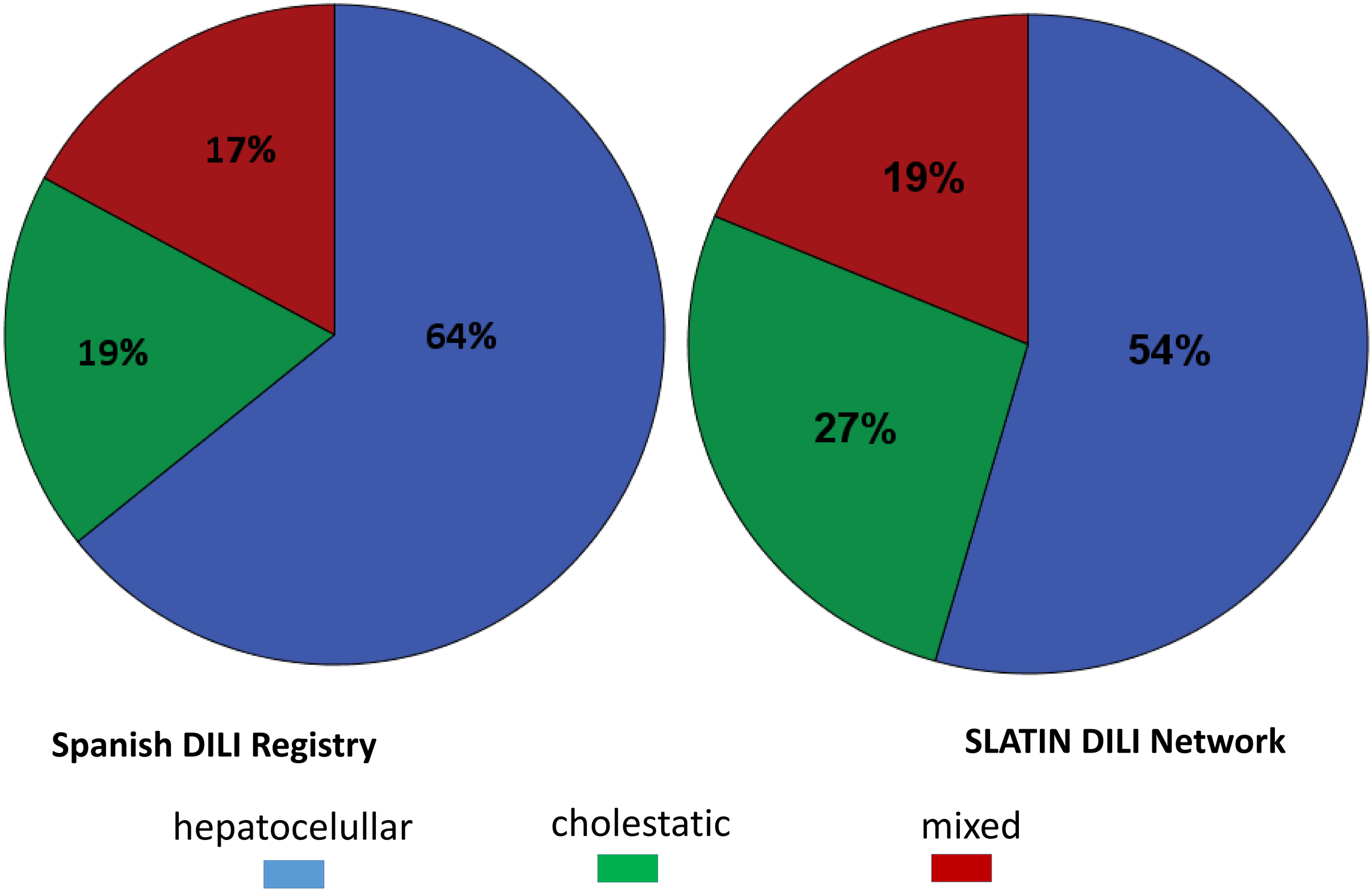

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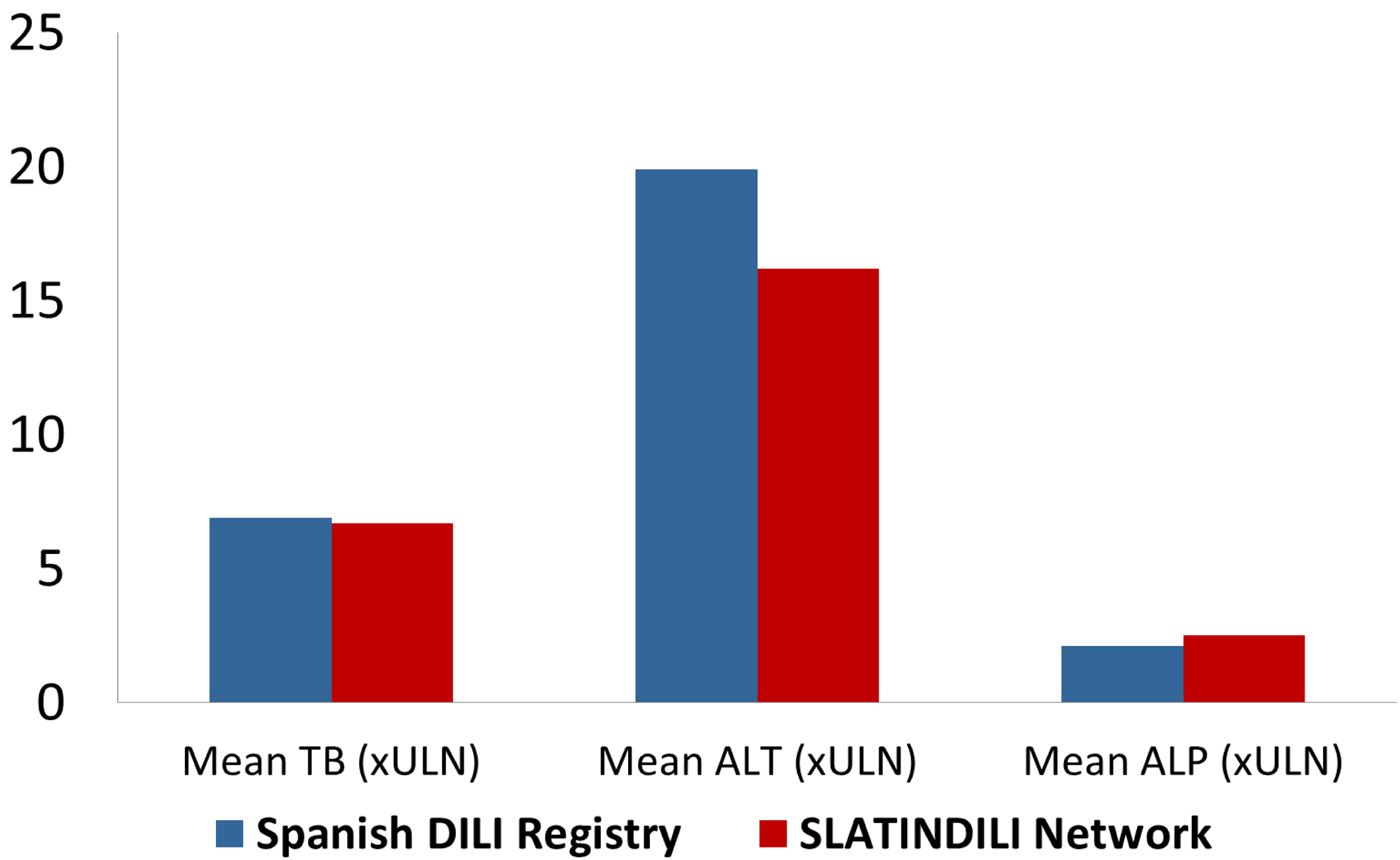

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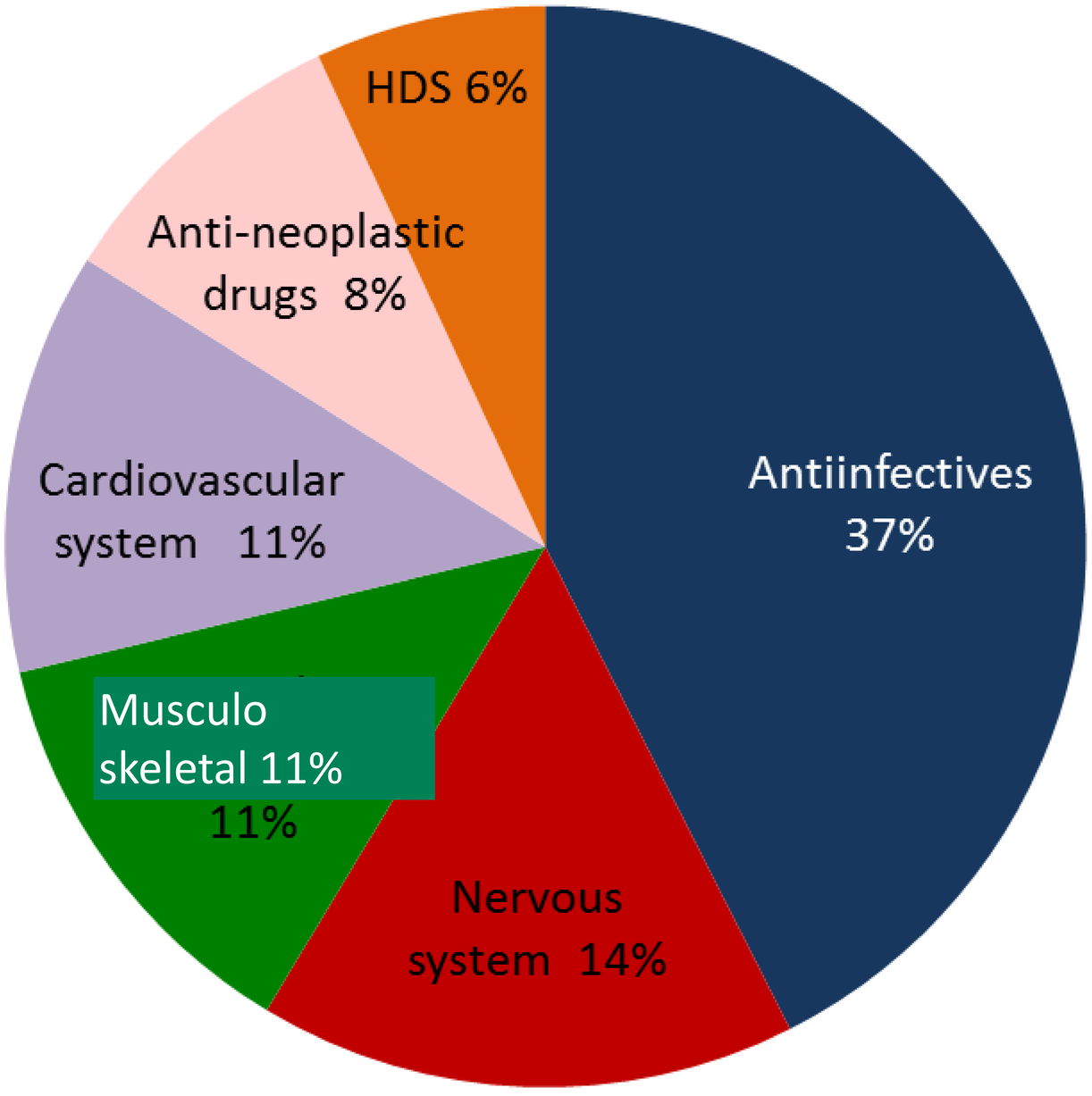
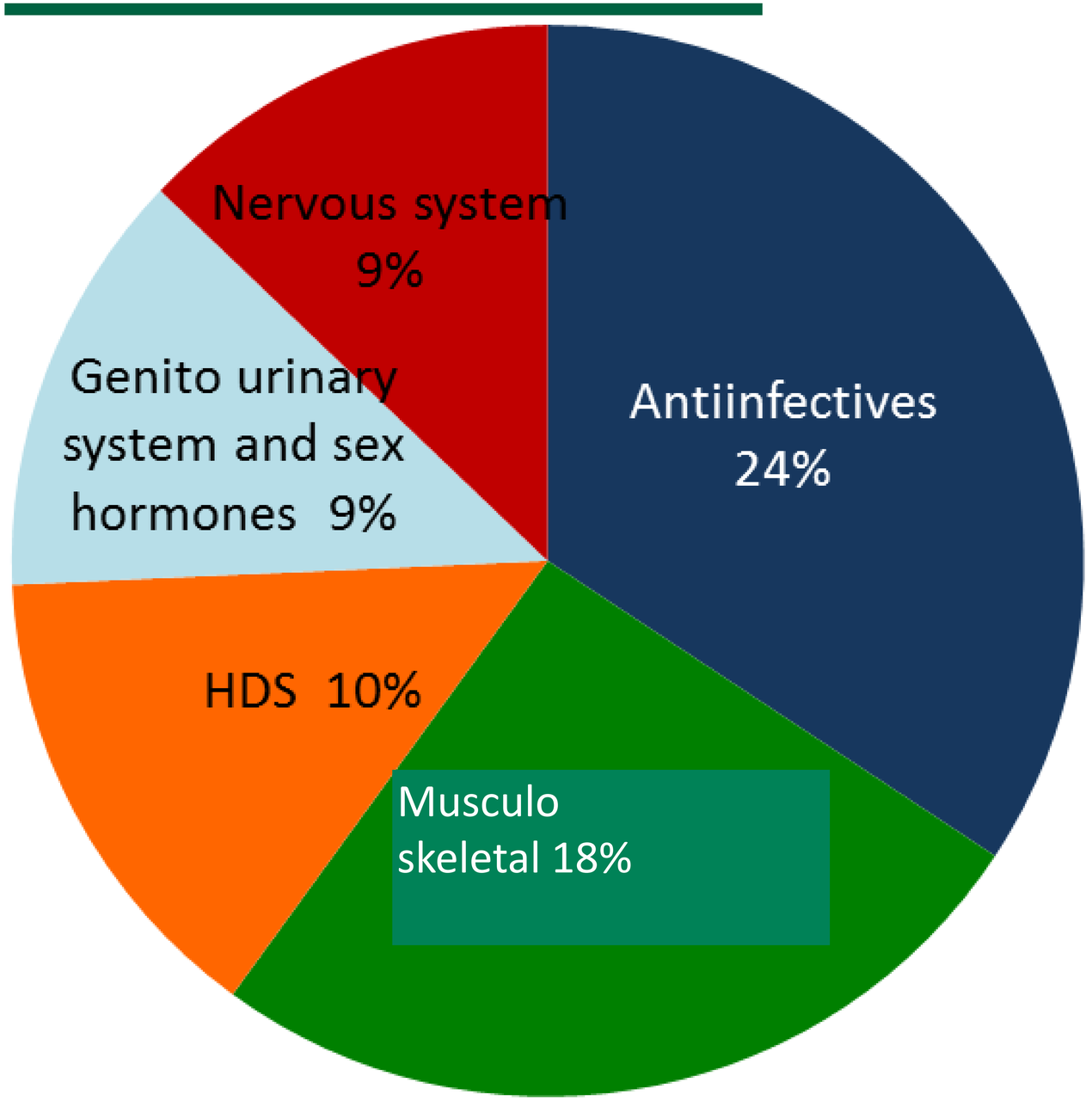


Spanish DILI Registry



SLATINDILI Network

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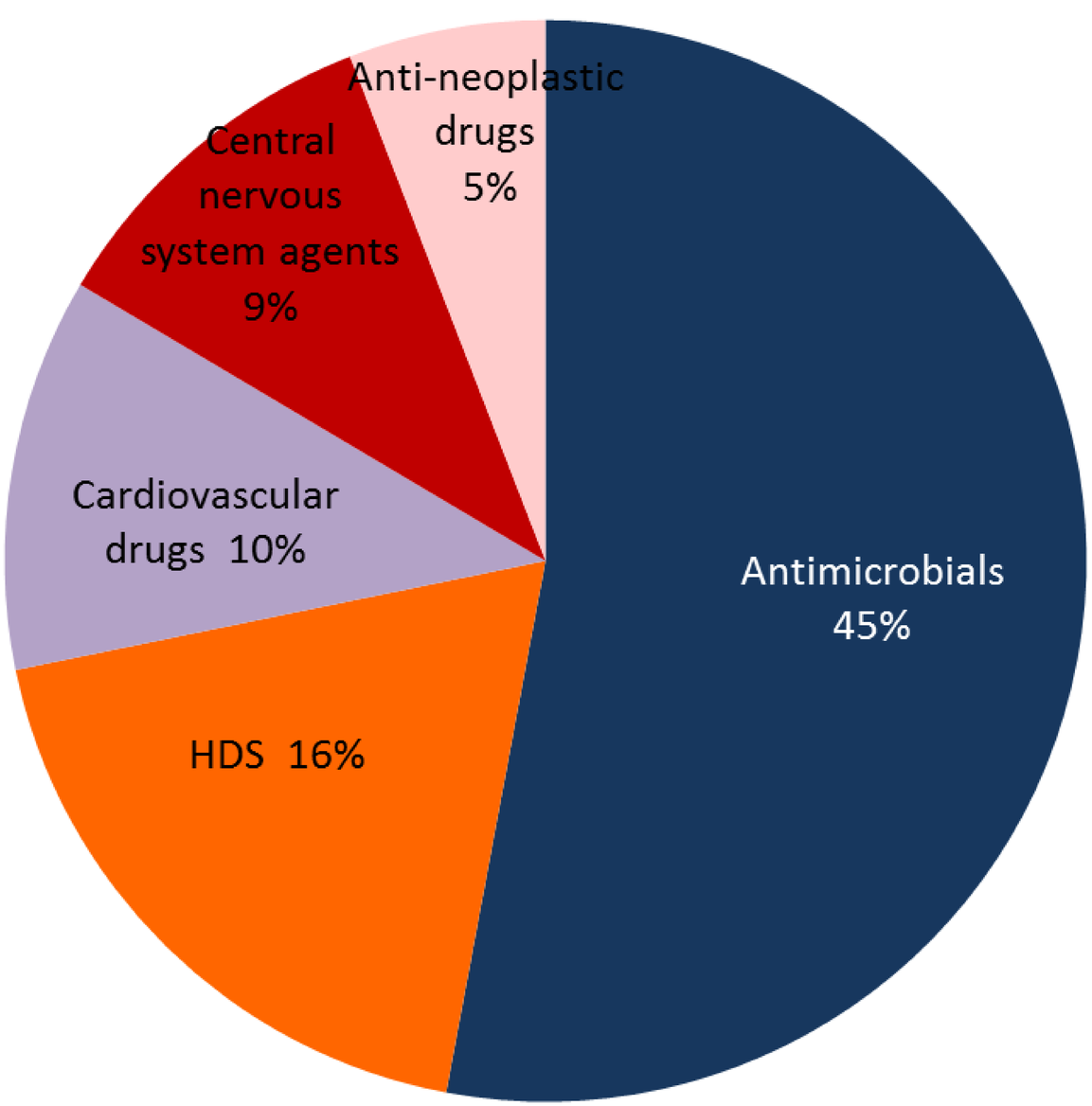
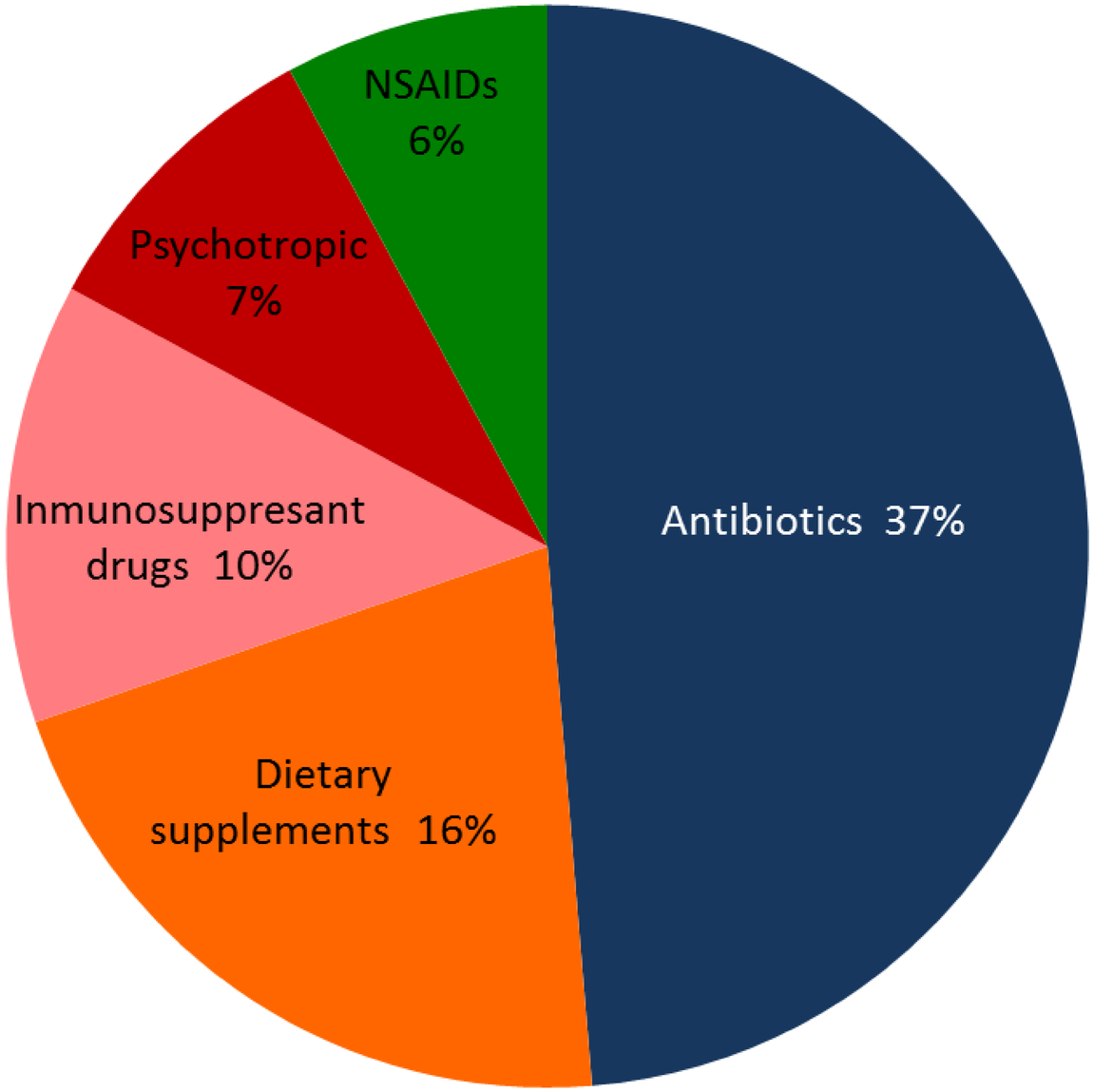


DILIN ***(Chalasani et al, Gastroenterology 2015)***



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