

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

F Bessone¹, N Hernández², A Sánchez², M Di Pace², G Gualano³, M Arrese⁴, A Ruiz⁴, A Loeza del Castillo⁵, M Giralá⁶, E Carrera⁷, M Lizarrábal⁸, E Mengual⁸, J Brahm⁹, JP Arancibia⁹, FC Tanno¹, M Davalos¹⁰, R Parana¹¹, MI Schinoni¹¹, N Méndez-Sánchez¹², M Garassini¹³, RL Zapata¹⁴, I Medina-Cáliz¹⁵, A González-Jiménez¹⁵, M Robles-Díaz¹⁵, C Stephens¹⁵, A Ortega¹⁵, J Sanabria¹⁵, M García-Cortés¹⁵, B Garcia-Muñoz¹⁵, MI Lucena¹⁵, RJ Andrade¹⁵

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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).

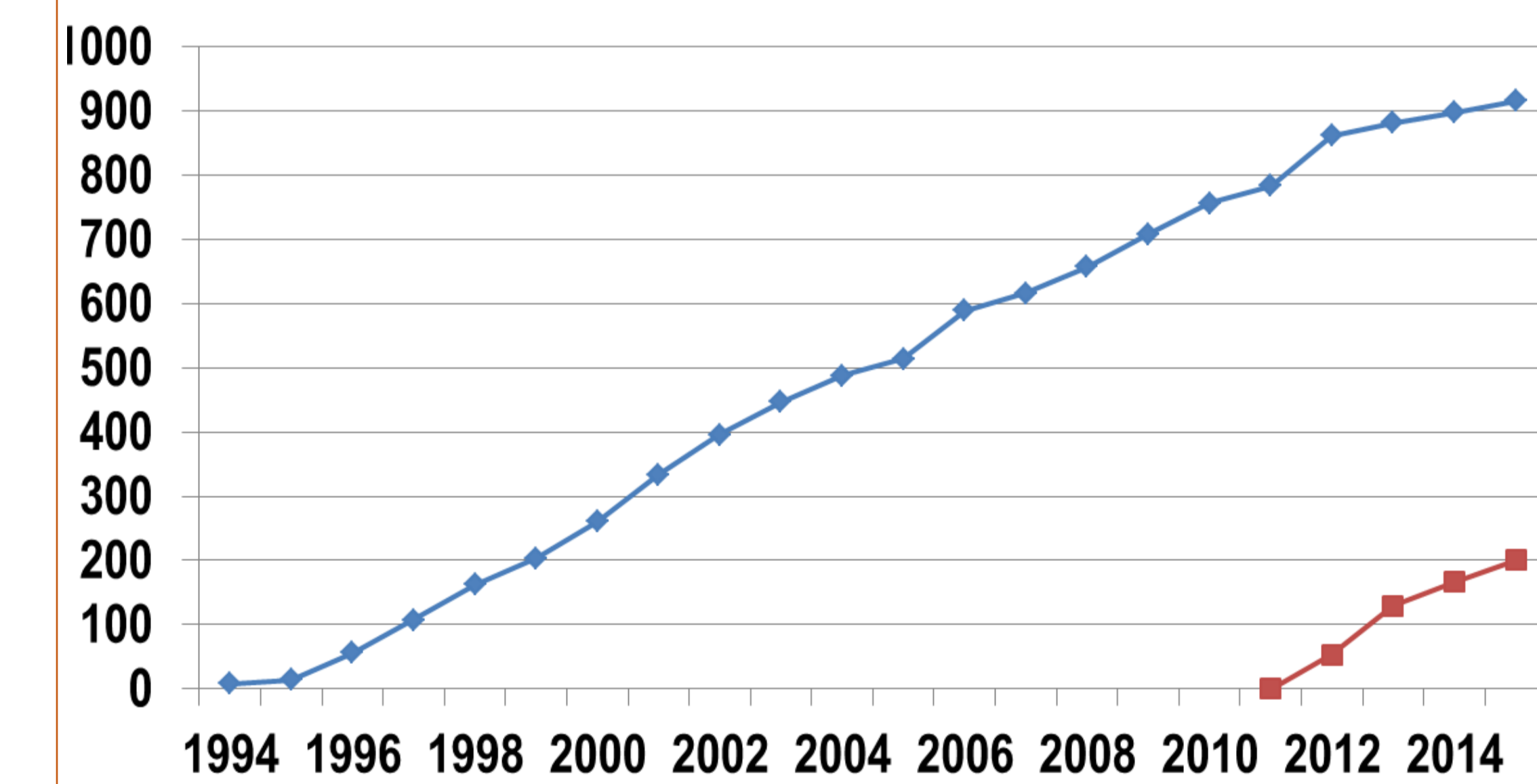


Figure 1. Case enrolments in the Spanish DILI Registry (◆) and SLATINDILI Network (■)

Table 2. Main drugs in both the Spanish and Latin American 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 | SLATINDILI 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(%) | | | |
| Mild+moderate | 742 (88) | 170 (86) | 0.6 |
| Severe | 63 (8) | 18 (9) | |
| Fatal | 36 (4) | 10 (5) | |
| Outcome, n(%) | | | |
| FHF-OLT | 20 (2) | 5 (2.5) | 0.9 |
| FHF-death | 16 (2) | 5 (2.5) | 0.5 |
| Time to resolution, mean (range) | 130 | 65 | <0.001 |

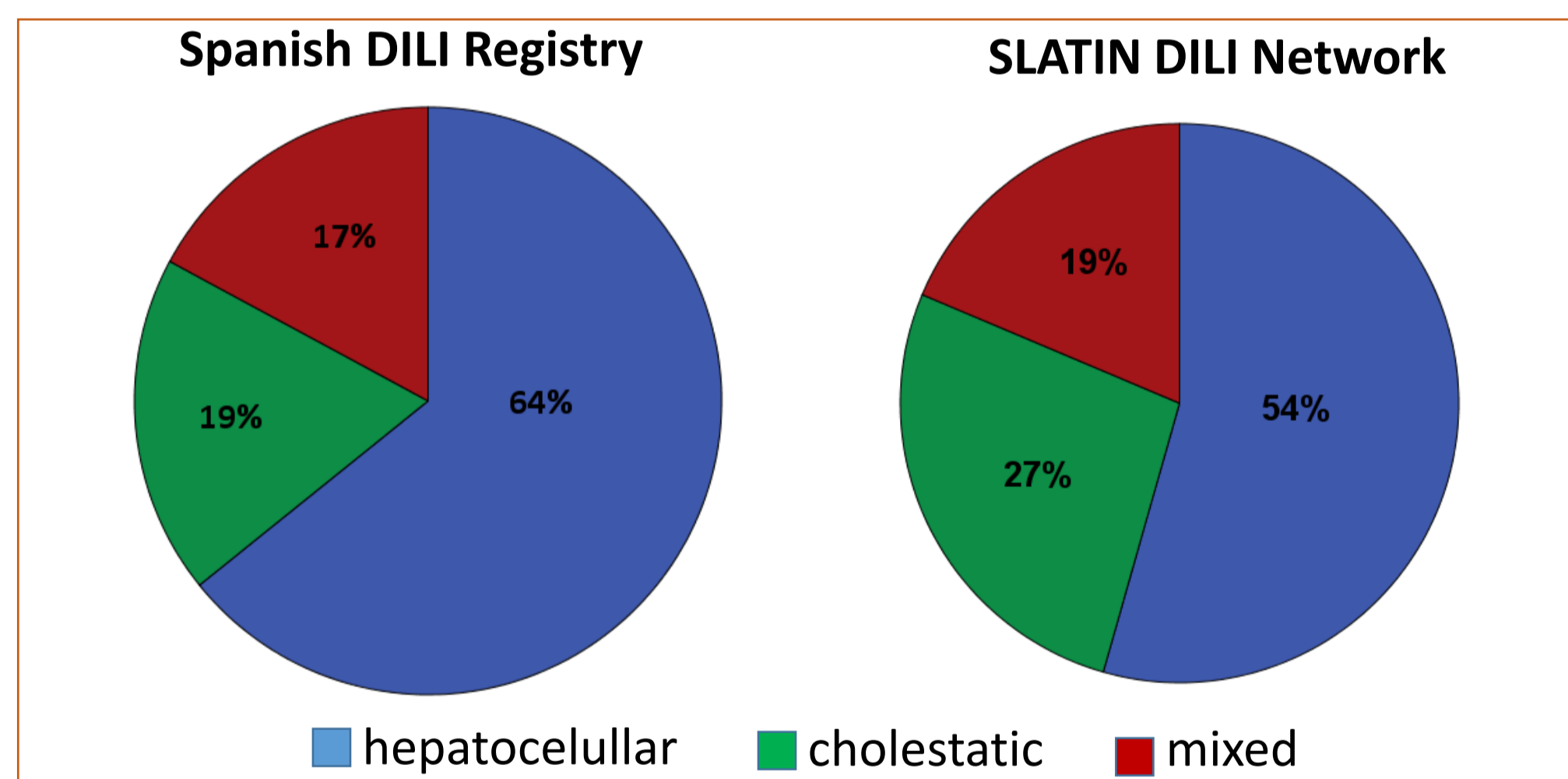


Figure 3. Type of liver injury in spanish vs latinamerican cases

The mean age of DILI development differed between the two registries with 51 years in Latin America and 54 years in Spain ($p=0.02$) (Table 1, Figure 2). Females predominated among the Latin American cases (59%) compared to the Spanish cases (49%) ($p=0.01$). Duration of treatment and time to onset were higher in Latin American 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 Latin American cohort. Amoxicillin-clavulanate, diclofenac, nimesulide, and nitrofurantoin were the most common causatives in Latin America, and amoxicillin-clavulanate, antituberculosis treatments, ibuprofen and atorvastatin in Spain (Table 2). Herbal and dietary supplements for bodybuilding DILI were more represented in Latin America (10% vs 6%, $p=0.05$).

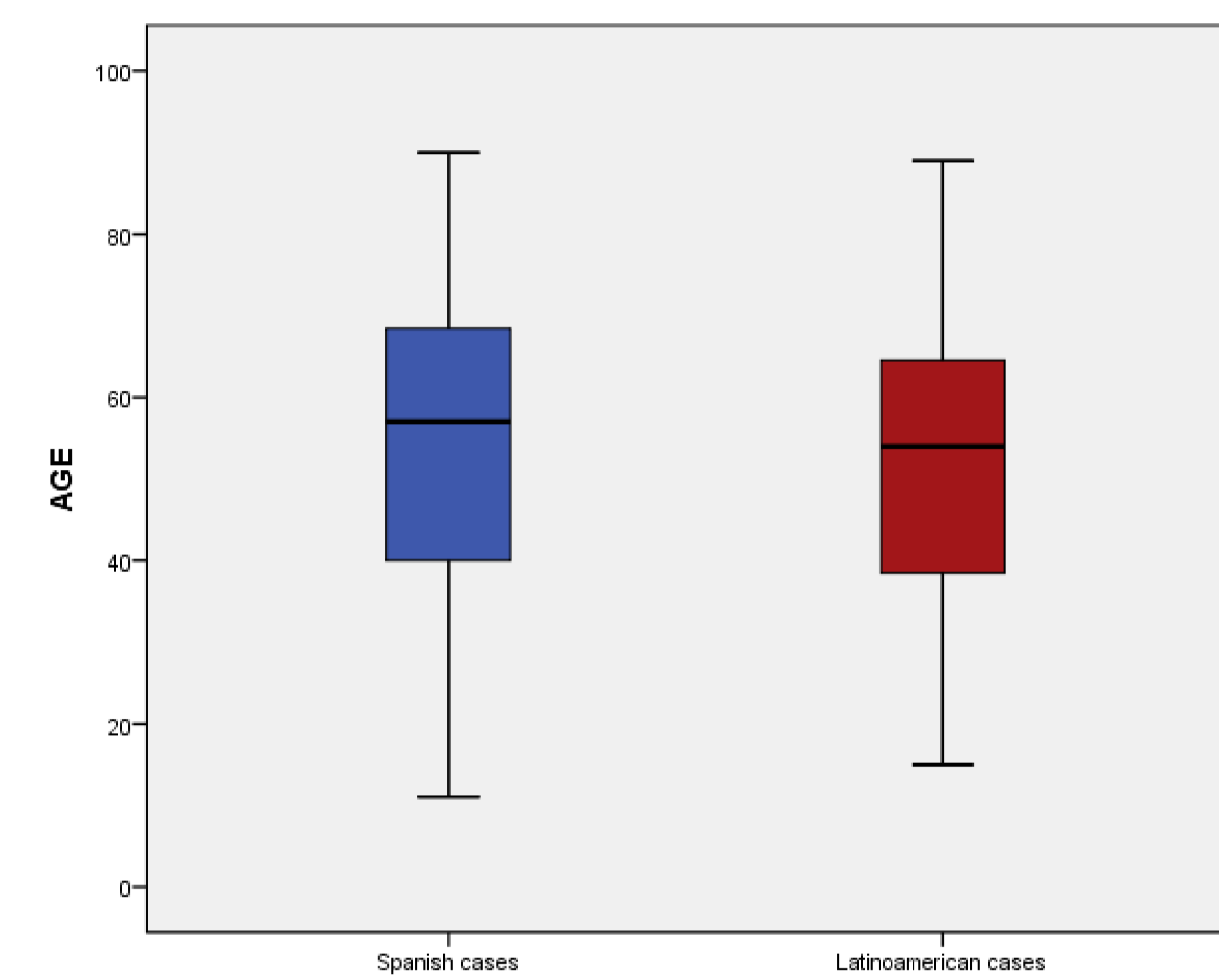


Figure 2. Distribution by age in spanish vs latinamerican cases

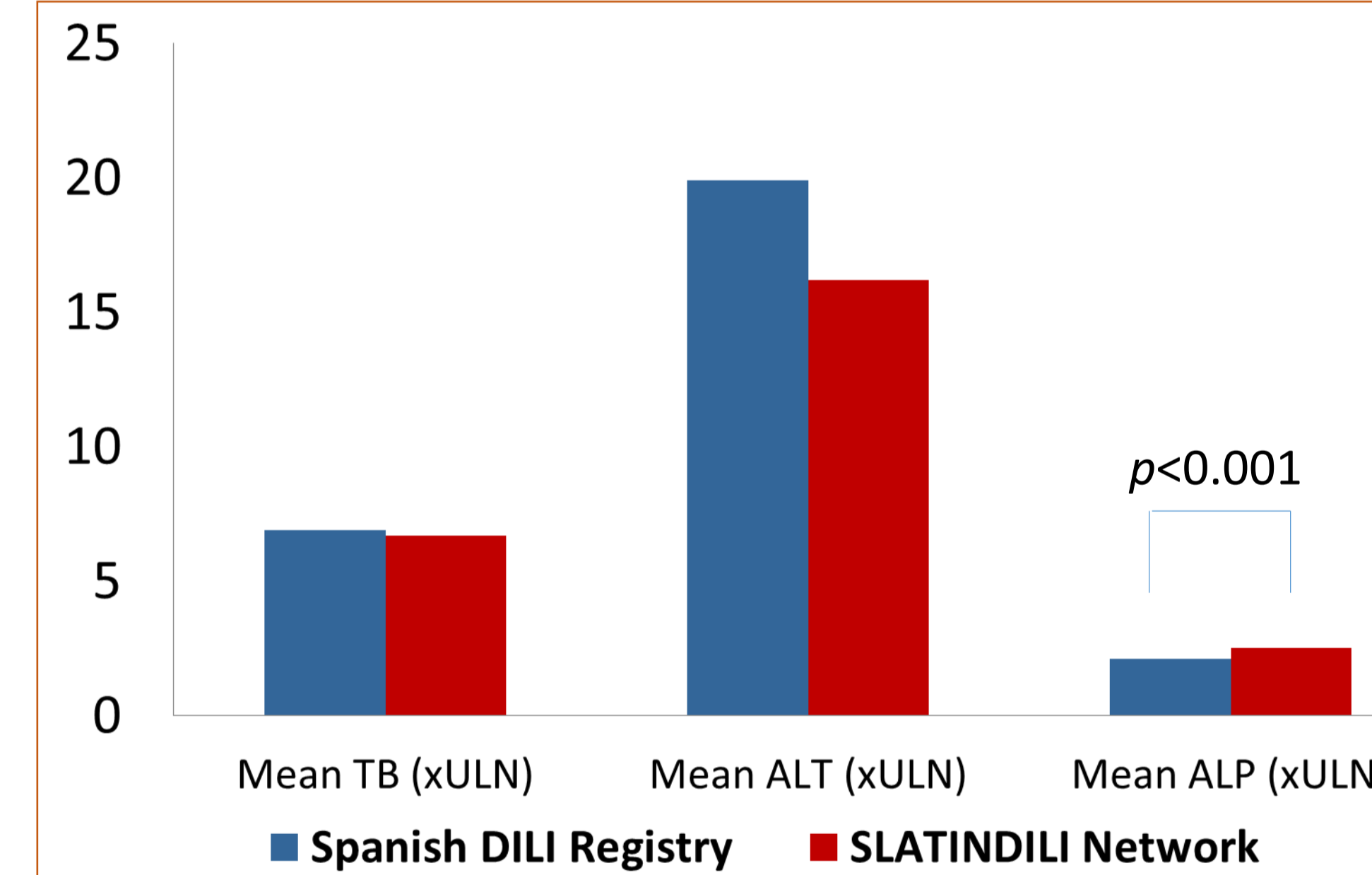


Figure 4. Laboratory parameters at onset in spanish vs latinamerican cases

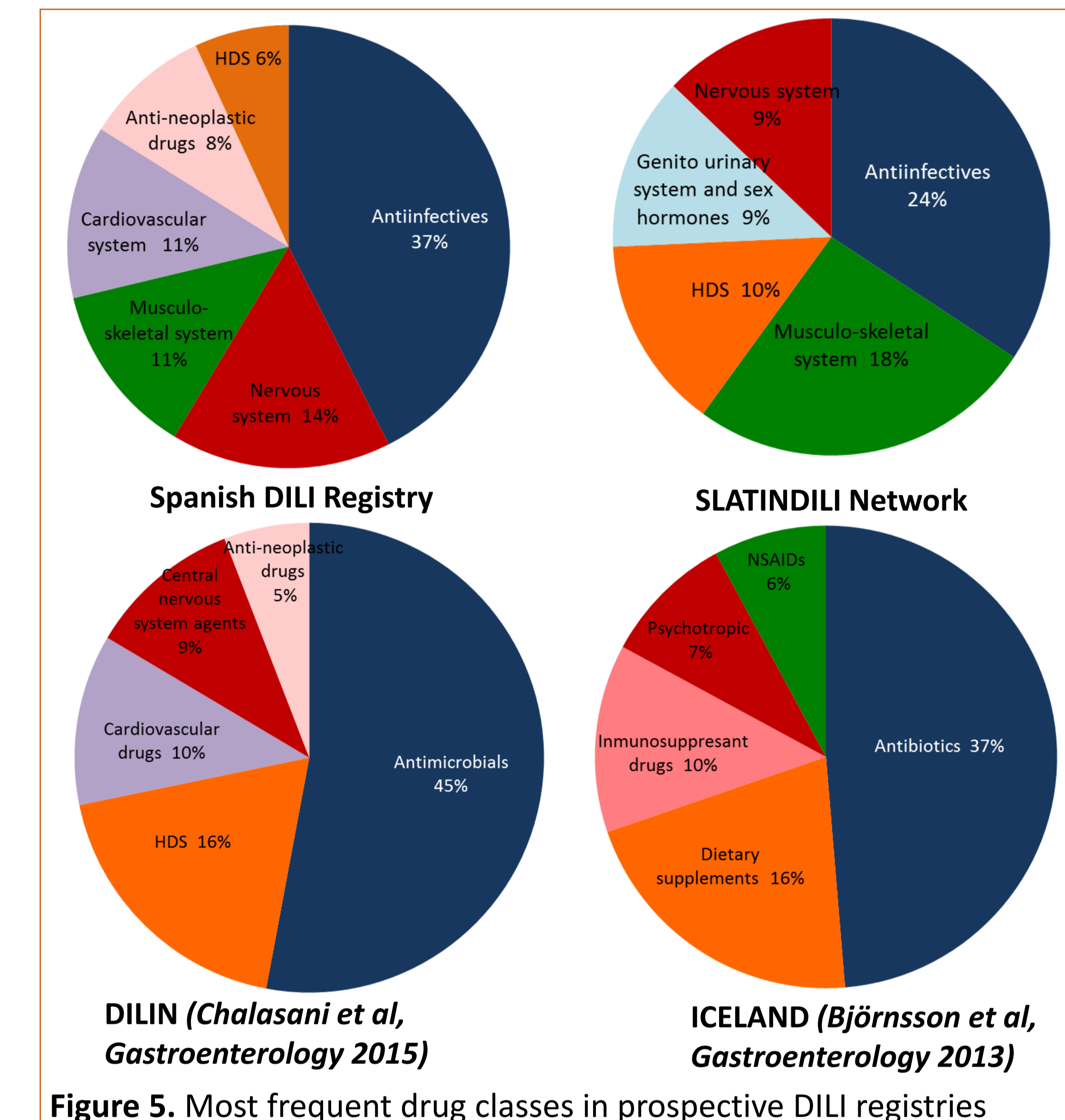


Figure 5. Most frequent drug classes in prospective DILI registries

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.

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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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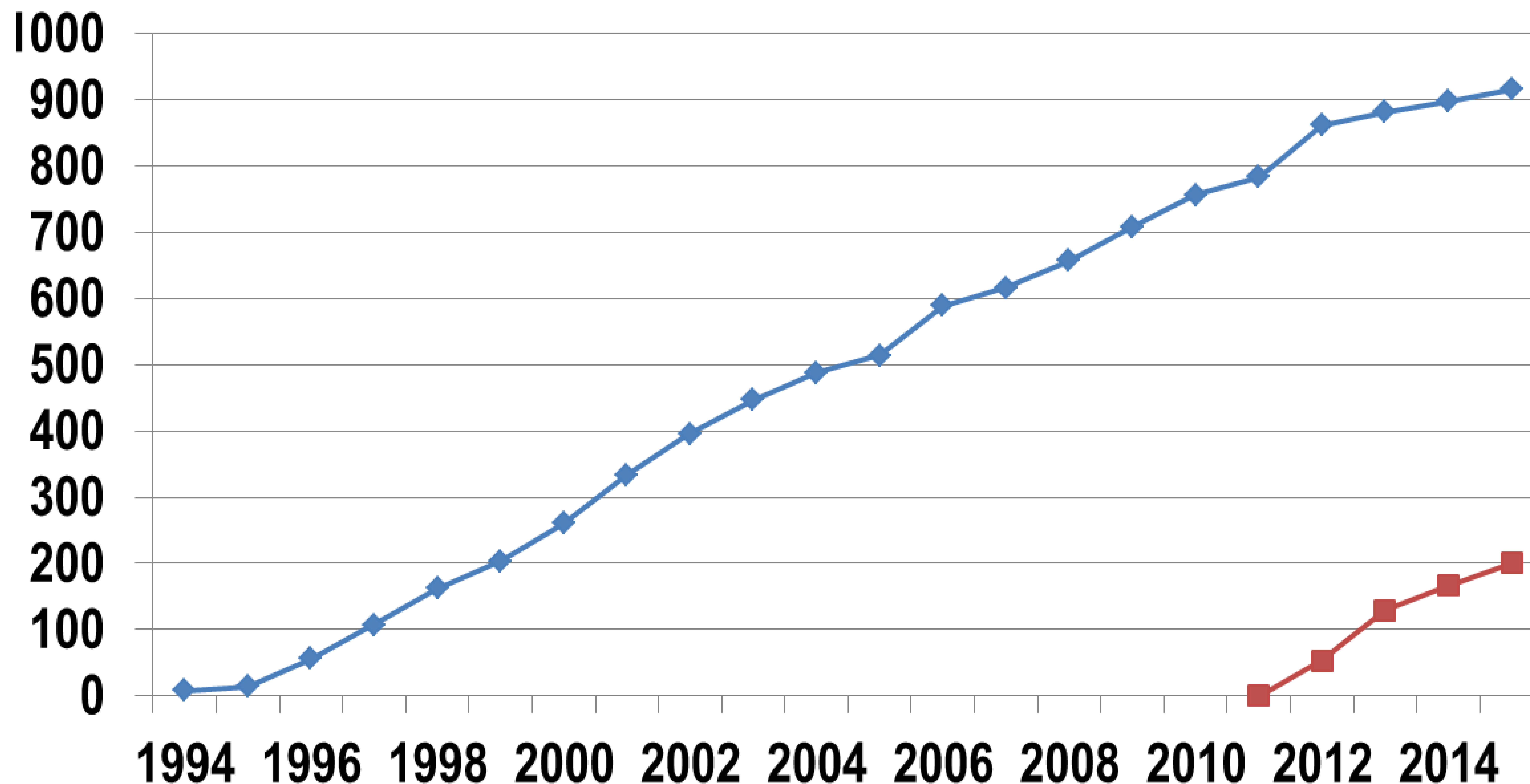
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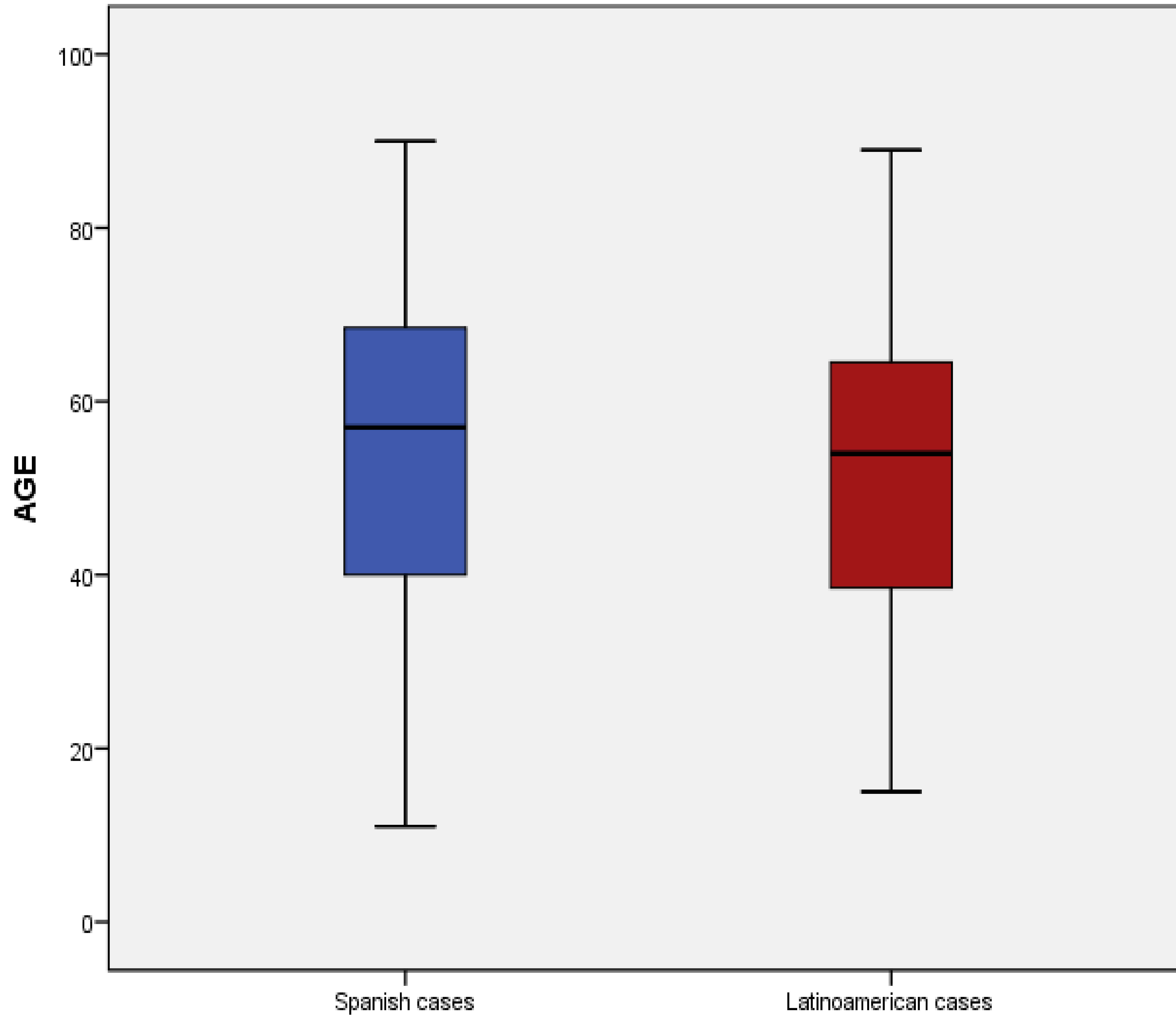
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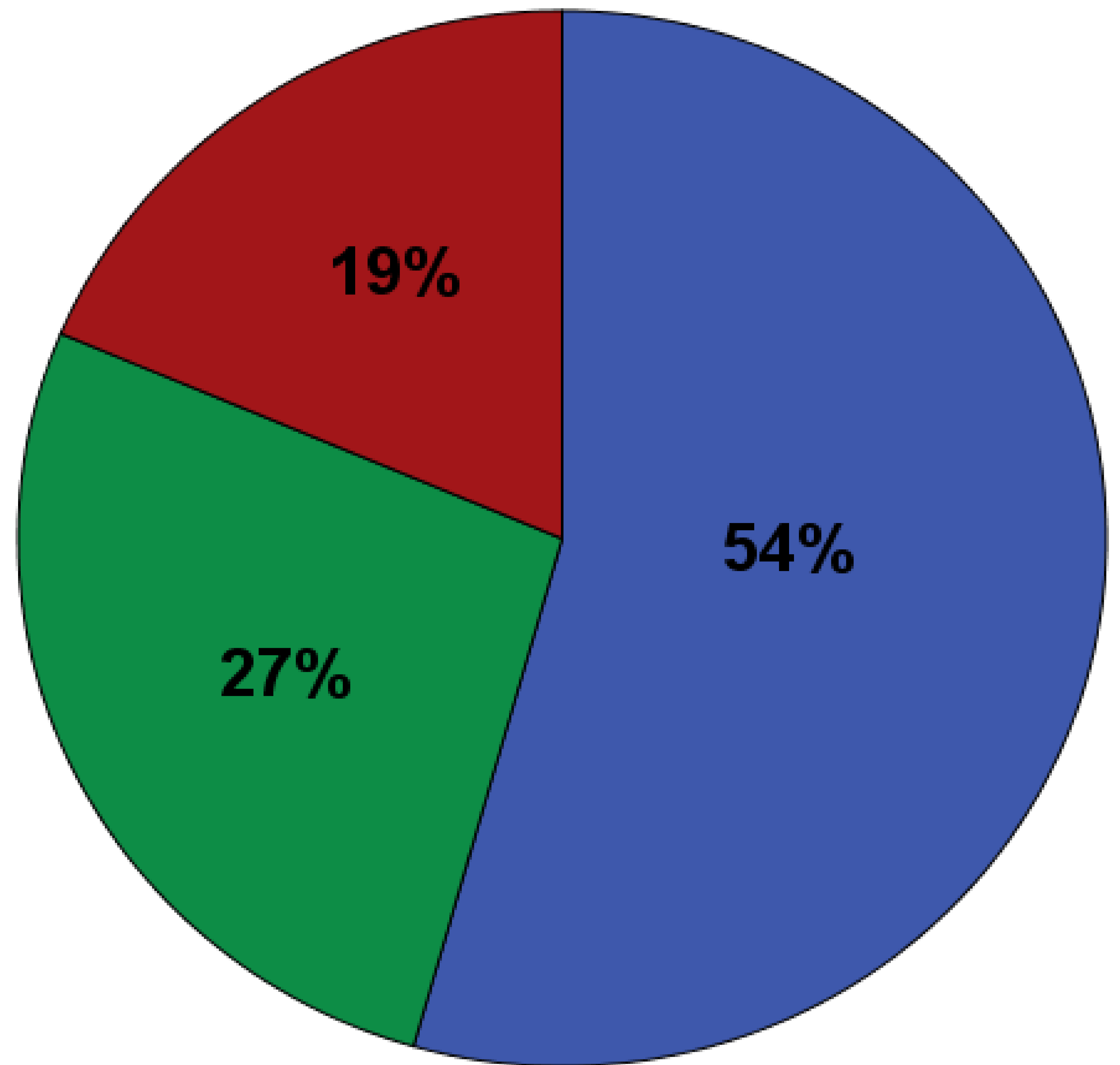
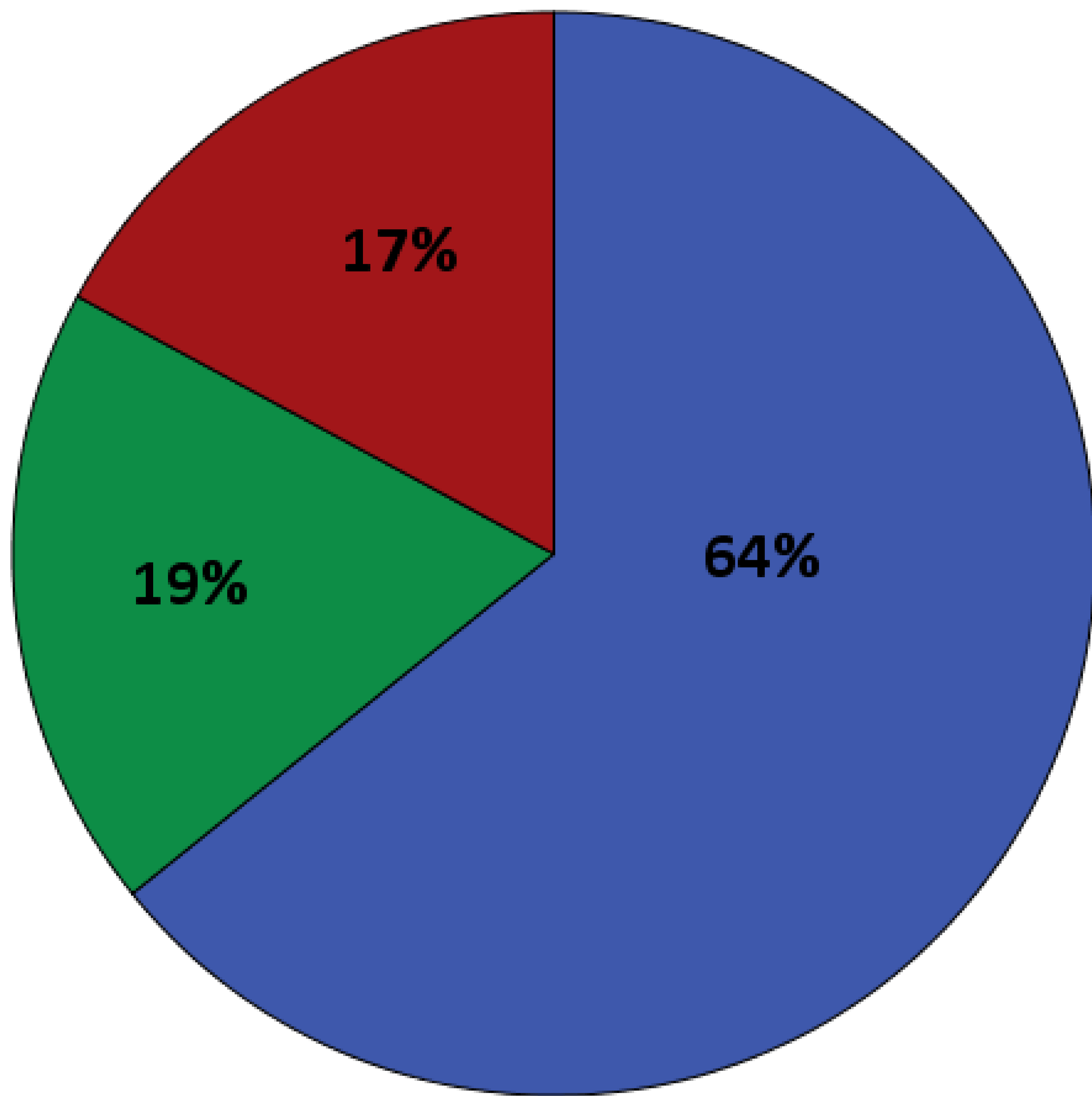
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Spanish DILI Registry

SLATIN DILI Network

hepatocelullar

cholestatic

mixed

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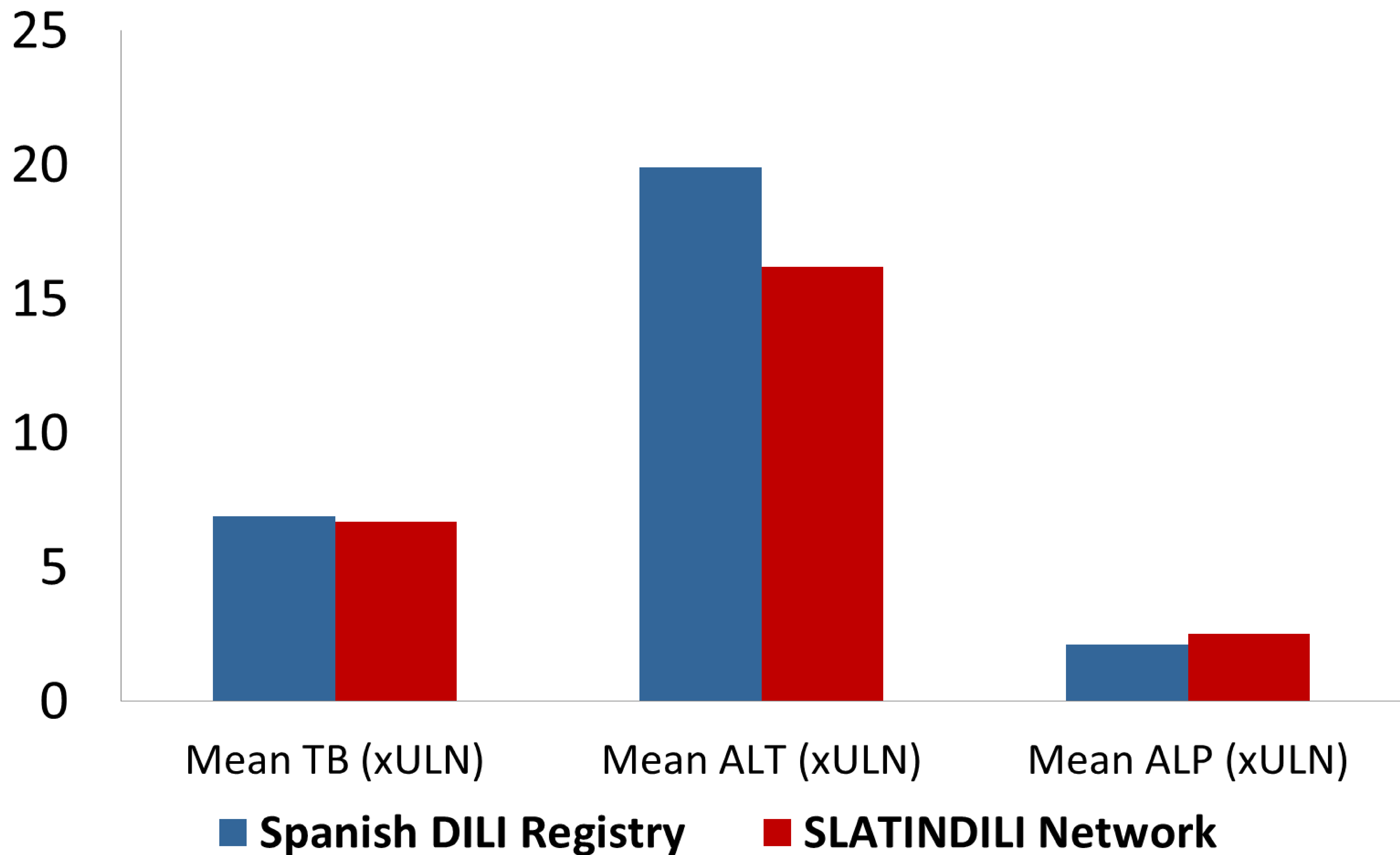
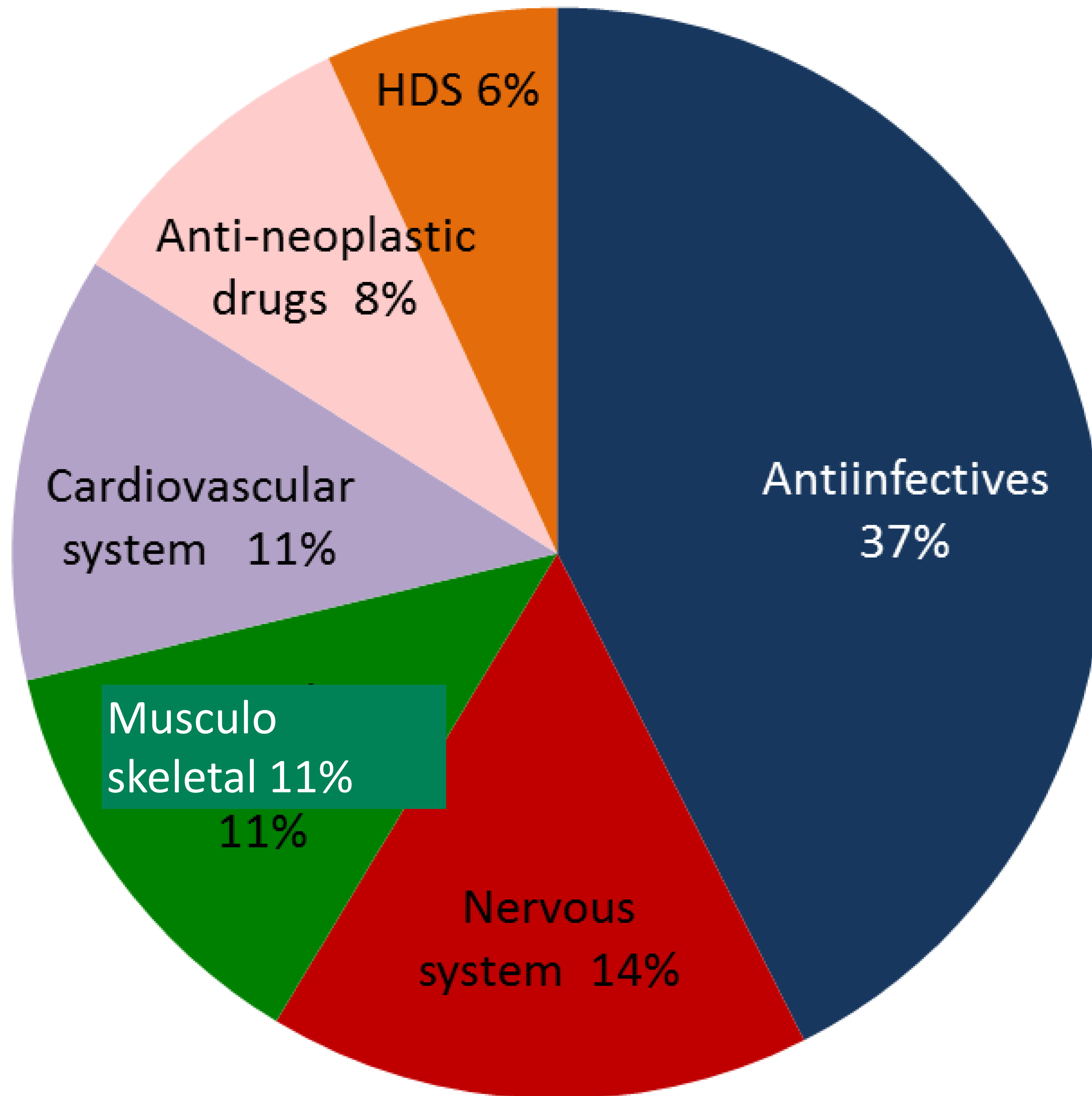
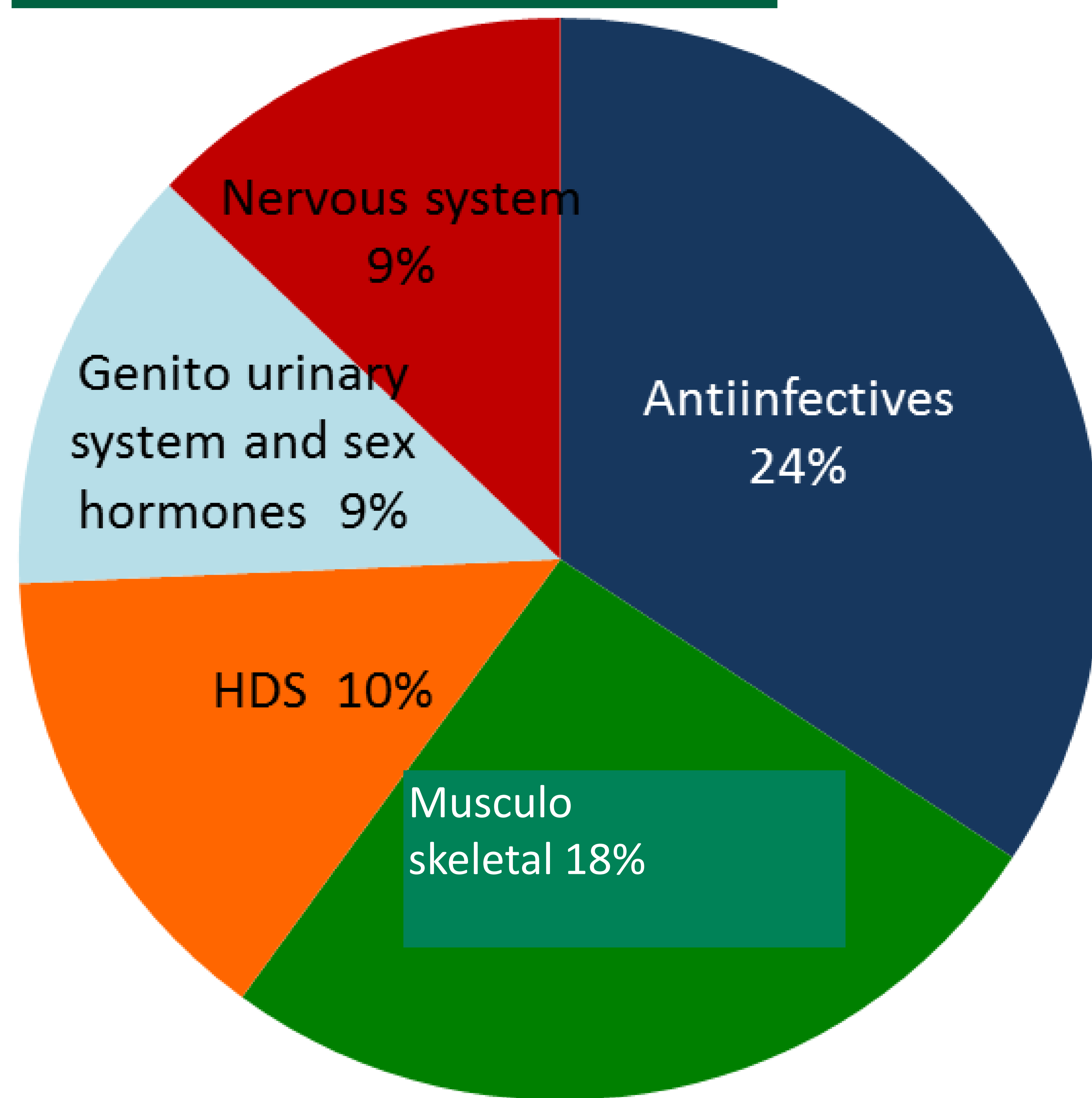


Figure 5. Most frequent drug classes in prospective DILI registries

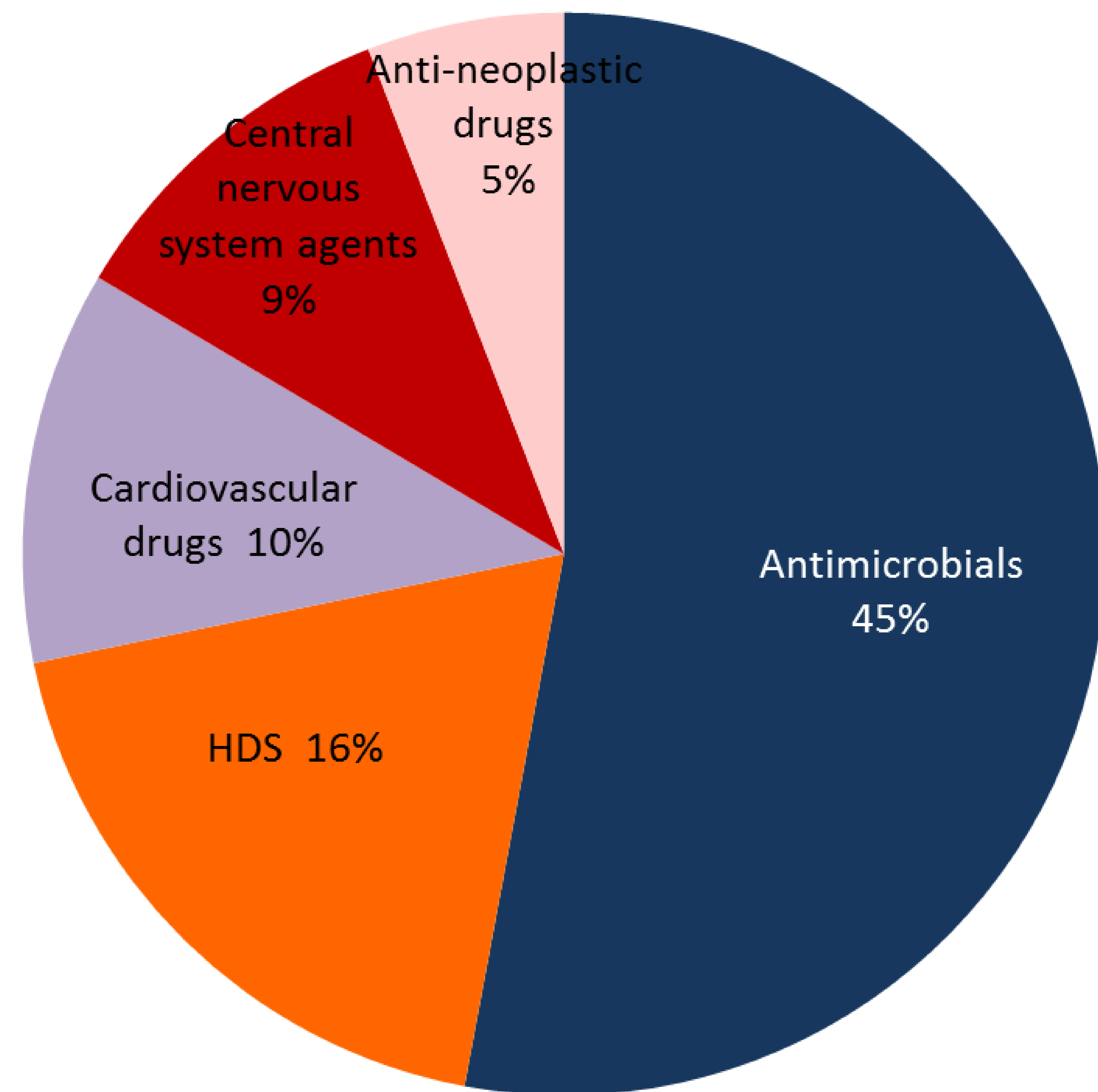


Spanish DILI Registry

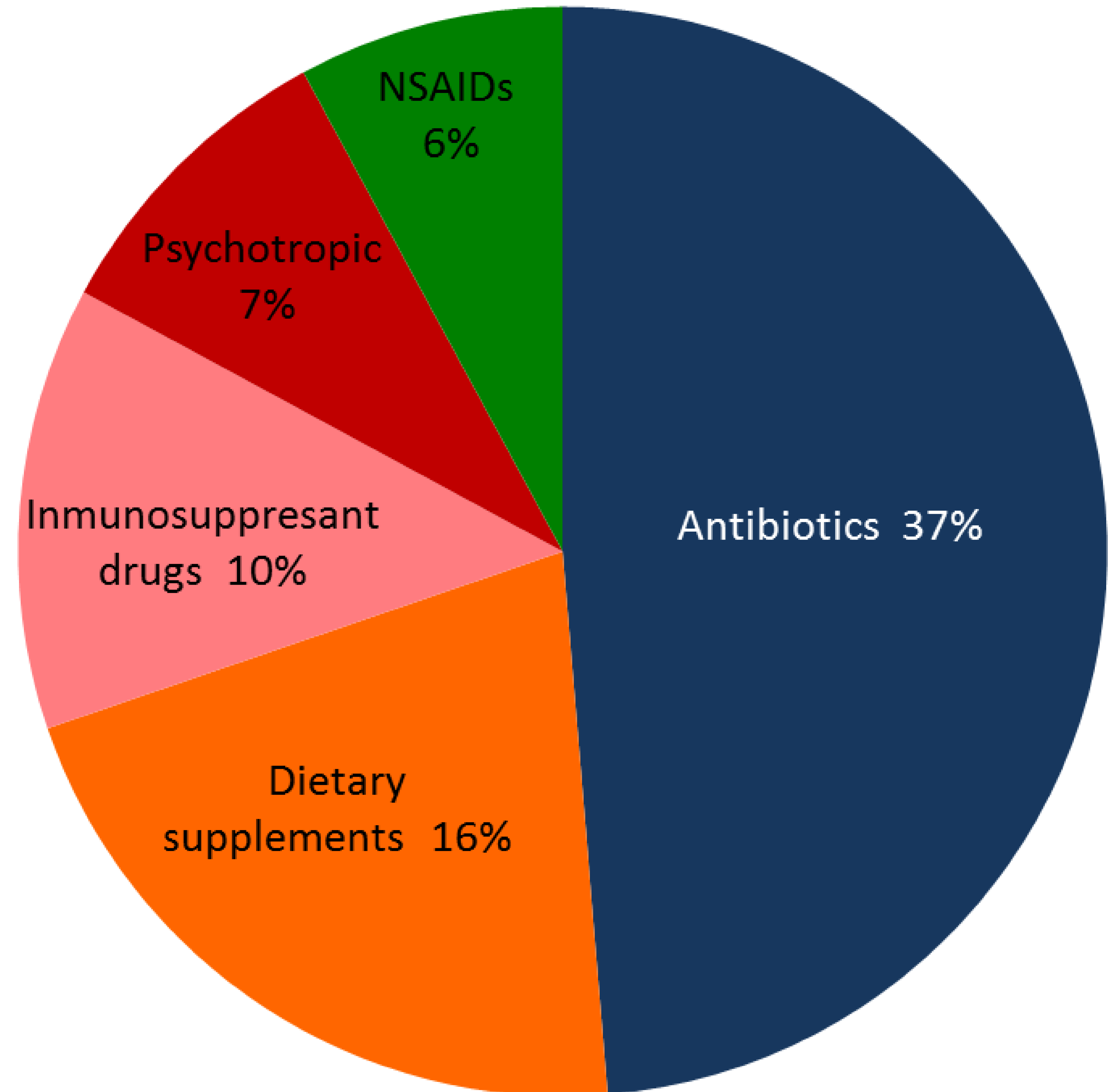


SLATINDILI Network

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DILIN (Chalasani et al, Gastroenterology 2015)



ICELAND (Björnsson et al, Gastroenterology 2013)

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