

Epidemiological and clinical profile of HDV infected people in care in Italy: interim analysis from the ongoing PITER cohort

L.A. KONDILI¹, M.E. TOSTI¹, M.G. QUARANTA¹, A. CIANCIO², V. MESSINA³, G. BRANCACCIO⁴, M.R. BRUNETTO⁵, M. CAPASSO⁶, V. ROSATO⁷, I. CACCIOLA⁸, L. PASULO⁹, T.A. SANTANTONIO¹⁰, C. COPPOLA¹¹, E. BILIOTTI¹², F. BARBARO¹³, M. MASSARI¹⁴, N. COPPOLA¹⁵, A. FERRARESE¹⁶, F.P. RUSSO⁴, V. DI MARCO¹⁷, A. MARRONE¹⁵, S. SCHIVAZZAPPA¹⁸, A. FEDERICO¹⁵, P. BLANC¹⁹, A. ROCCO⁶, G. MORSICA²⁰, D. IELUZZI²¹, F. CONTI²², M. DE SIENA²³, M.G. BAVETTA²⁴, M. MILELLA²⁵, I. GENTILE⁶, C. PORCU²⁶, L. CHEMELLO⁴, M. MARRACCI²⁷, A.L. ZIGNEGO²⁸, L. BAIOCCHI²⁹, I. MAIDA³⁰, B. COCO⁵ on behalf of PITER Collaborating Group*

1Istituto Superiore di Sanità, Rome; 2Città della Salute e della Scienza di Turin, University Hospital, Turin; 3Sant'Anna Hospital, Caserta; 4University of Padua; 5University Hospital of Pisa; 6Federico II University, Naples; 7Betania Hospital, Naples; 8University Hospital of Messina; 9Papa Giovanni XXIII Hospital, Bergamo; 10Ospedali Riuniti, Foggia; 11Gragnano Hospital, Gragnano (NA); 12Lazzaro Spallanzani-IRCCS, Rome; 13University Hospital of Padua; 14Azienda Unità Sanitaria Locale, IRCCS di Reggio Emilia; 15University of Campania "Luigi Vanvitelli", Naples; 16University Hospital Borgo Trento, Verona; 17University of Palermo; 18University of Parma; 19Santa Maria Annunziata Hospital, Florence; 20San Raffaele Hospital, Milan; 21University Hospital of Verona; 22Hospital of Faenza, A.U.S.L. of Romagna; 23Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome; 24Villa Sofia-Cervello Hospital, Palermo; 25University Hospital Policlinico, Bari; 26University Hospital, Monserrato, Cagliari; 27Polytechnic University of Marche, Ancona; 28University of Florence; 29University of Tor Vergata, Rome; 30University of Sassari, Sassari; Italy - *available in www.progettopiter.it



Introduction

With the new therapeutic options available for hepatitis Delta infection (HDV), epidemiological and clinical profile of patients in care are useful to determine better treatment appropriateness.

Aim

We aimed to describe the updated epidemiological and clinical profile of HDV infected patients in the PITER HBV cohort.

Method

Study population: Patients consecutively enrolled in PITER between October 2019 and February 2022, were analyzed. PITER is an observational cohort study that enrolled consecutive HBsAg-positive patients seen in 59 infectious disease or gastroenterology/hepatology clinical centers; the participating centers were well distributed over Italy. The inclusion criteria were consecutive patients with HBsAg positivity for at least 6 months with or without co-infection with HDV and/or HCV, independently of antiviral treatment. The exclusion criteria were patients with previous HBV infection who were HBsAg negative at enrolment, acute HBV hepatitis. The virological and routine analyses were performed at each participating centre using standard commercial kits. **Statistical Analysis:** The Mann-Whitney U test was used for continuous variables to assess differences between distribution, and the Chi-squared test was used to compare proportions. A p value <0.05 was considered statistically significant. Statistical analysis was performed with STATA version 16.1 (StataCorp, College Station, TX, USA).

Conclusions

- The prevalence of anti-Delta in the PITER HBV/HDV cohort of HBsAg-positive patients is 9.8%
- More than 20% of HBsAg-positive patients have never been tested for anti-HDV
- Of anti-HDV positive patients, 38% have never been tested for HDV RNA
- Of HDV RNA tested patients, 66% were HDV RNA positive.
- The updated picture of patients in care in Italy confirms the older Italian cohort and significantly younger non-Italian cohort of patients in care with HDV infection, both with a significant proportion of liver cirrhosis.
- Despite being almost a decade younger than Italians, about 60% of the non-Italian natives in care had liver cirrhosis.
- The dysmetabolic comorbidities are more represented in Italians, but the overall comorbidity profile is similar between two cohorts.
- The comorbidity profile detected in patients co-infected with Delta virus calls for attention to consider their role in patients' eligibility for future treatments employing the use of interferon.

Acknowledgements

The authors wish to thank all PITER collaborating group and all participating centers, investigators and research staff (available in www.progettopiter.it) who are involved in the study on a voluntary basis, for their time and effort. We also thank Giampaolo La Terza (Medisoft Informatic Services) for Database maintenance and implementation. We additionally acknowledge Federica Magnani, Rosangela Duranti, Erika Olivieri, Alessandra Mattei for secretarial and administrative assistance.

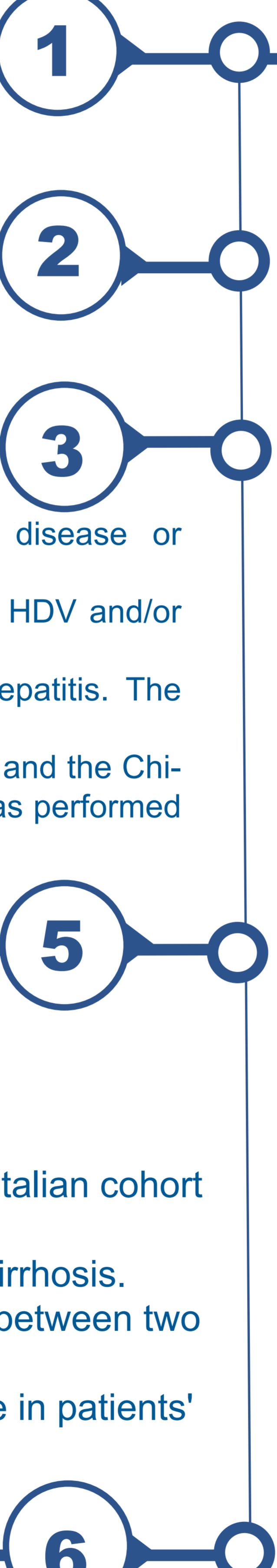
References

- Kondili LA, Vella S; PITER Collaborating Group. Dig Liver Dis. 2015;47:741-3. doi: 10.1016/j.dld.2015.05.022.
- Brancaccio G. et al. Int J Infect Dis. 2023;129:266-273. doi: 10.1016/j.ijid.2023.02.006.

Contact information

Loreta Kondili MD, PhD. Center for Global Health, Istituto Superiore di Sanità, Rome. Email: loreta.kondili@iss.it

Results



Characteristics of HBV and HBV/HDV coinfecting patients by Italian and non-Italian origin

Of 5490 patients of whom 1233 (22.4%) were non-Italian natives, the anti-HDV prevalence was 9.8% (424 of 4306 anti-HDV tested patients): 8.5% (median age 58; IQR 32-83) Italian, 14.1% (median age 44 years IQR 36 - 55 years) non-Italian natives (p<0.001); 21.5% (1184 of 5490) have never been tested for HDV infection (22.3% in Italian and 18.4% in non-Italian; p<0.001), of whom 21.0% (249 of 1184) with liver cirrhosis. Of anti-HDV positive patients, 259 (61.1%) were tested for HDV RNA, of whom 164 (63.3%) were HDV RNA positive. HBV/HDV coinfecting patients of non-Italian origin are significantly younger than Italian patients (p<0.001) (Figure 1) and with a significantly higher prevalence of females, p<0.001 (potentially by HBV screening in younger ladies) (Figure 2). Characteristics of HBV/HDV coinfecting versus mono-infected HBV chronic hepatitis patients are shown in Table 1. Of anti-HDV positive patients, ALT and AST levels were altered in 60.4% and 58.7 patients, respectively; cirrhosis was present in 69.8% of patients (75.2% in Italian and 59.2% in non-Italians; p=0.001).

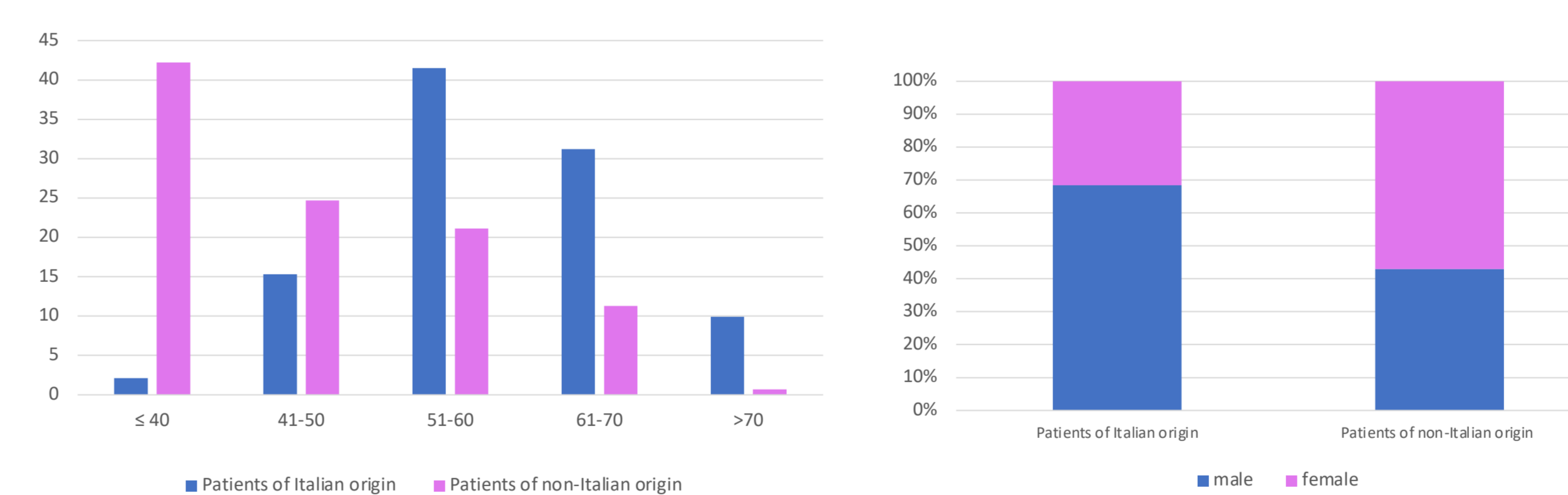


Figure 1. HDV infection in Italian vs non-Italian patients by age

Figure 2. HDV infection in Italian vs non-Italian patients by gender

| | HBV/HDV coinfecting patients | | | HBV mono-infected patients | | |
|--------------------|--------------------------------------|--|-----------------|---------------------------------------|--|------------------|
| | Patients of Italian origin N=282 (%) | Patients of non-Italian origin N=142 (%) | Total N=424 (%) | Patients of Italian origin N=3019 (%) | Patients of non-Italian origin N=863 (%) | Total N=3882 (%) |
| Elevated serum ALT | 168 (59.6) | 88 (62.0) | 256 (60.4) | 544 (18.0) | 351 (22.1) | 735 (18.9) |
| Elevated serum AST | 167 (59.2) | 82 (57.8) | 249 (58.7) | 567 (18.8) | 355 (22.0) | 722 (18.6) |
| Cirrhosis | 212 (75.2) | 84 (59.2) | 296 (69.8) | 774 (25.6) | 99 (11.5) | 873 (22.5) |
| Platelets <150,000 | 167 (61.2) | 63 (45.3) | 230 (56.1) | 570 (20.0) | 100 (12.1) | 670 (18.2) |
| Ascites | 27 (38.0) | 8 (36.4) | 35 (37.6) | 58 (22.9) | 3 (12.0) | 61 (21.9) |
| Encephalopathy | 11 (18.3) | 3 (15.0) | 14 (17.5) | 0 (0.0) | 26 (17.6) | 26 (6.8) |
| Variceal bleeding | 12 (19.7) | 1 (4.8) | 13 (15.8) | 26 (19.8) | 2 (12.5) | 28 (13.0) |
| Child | | | | | | |
| A | 145 (82.4) | 202 (84.2) | 524 (88.8) | 65 (89.0) | 65 (89.0) | 130 (89.0) |
| B | 25 (14.2) | 6 (9.4) | 31 (12.9) | 65 (11.0) | 7 (9.6) | 72 (10.9) |
| C | 6 (3.4) | 1 (1.6) | 7 (2.9) | 1 (0.2) | 1 (1.4) | 2 (0.3) |
| Fib-4 | | | | | | |
| <1.45 | 44 (16.3) | 60 (43.2) | 104 (25.4) | 1280 (46.4) | 646 (79.5) | 1926 (54.0) |
| 1.45-3.25 | 103 (38.1) | 43 (30.9) | 146 (35.7) | 1205 (43.7) | 342 (17.5) | 1547 (37.7) |
| >3.25 | 123 (45.6) | 36 (25.9) | 159 (38.9) | 271 (9.8) | 29 (3.1) | 300 (7.8) |
| HBV DNA | 60 (23.2) | 55 (40.1) | 115 (29.0) | 887 (30.5) | 477 (56.9) | 1364 (36.4) |
| Ongoing therapy | 221 (78.4) | 104 (73.2) | 325 (76.7) | 2166 (71.8) | 467 (54.1) | 2633 (67.8) |
| NUC/other | 210 (95.0) | 97 (83.3) | 307 (94.5) | 2148 (99.3) | 453 (97.6) | 2603 (99.0) |

Table 1. Characteristics of HBV/HDV coinfecting and mono-infected HBV patients. For some variables inconsistencies are due to missing values. *p value Chi-square test

Liver disease progression cofactors and comorbidities in HBV and HBV/HDV coinfecting patients by Italian and non-Italian origin

Liver disease progression cofactors in both cohorts of HBV/HDV coinfecting and HBV mono-infected patients according to nationality are shown in Table 2. The main cofactors of liver disease progression were present as follows: alcohol use in 33.2% (similar in Italians and non-Italians), HCV infection in 10.3% (14.6% in Italian and 1.6% in non-Italian, p<0.001), diabetes in 7.1% (9.6% in Italians and 2.1% in non-Italian, p=0.005). Overall, 52.4% of patients have no comorbidities, 41.5% have 1-2, and 6.1% have more than 2 comorbidities. Table 3 shows the comorbidities distribution in enrolled patients with chronic HDV infection according to the cirrhosis status, helpful to evaluate the appropriateness of IFN-free therapies in those patients.

| | HBV/HDV coinfecting patients | | | HBV mono-infected patients | | |
|--------------------------------|--------------------------------------|--|-----------------|---------------------------------------|--|------------------|
| | Patients of Italian origin N=282 (%) | Patients of non-Italian origin N=142 (%) | Total N=424 (%) | Patients of Italian origin N=3019 (%) | Patients of non-Italian origin N=863 (%) | Total N=3882 (%) |
| Alcohol | 78 (33.9) | 38 (31.9) | 116 (33.2) | 901 (34.1) | 286 (36.3) | 1187 (34.6) |
| Alcohol (>3 alcohol units/day) | 14 (20.3) | 7 (22.6) | 20 (21.3) | 94 (22.0) | 27 (11.4) | 121 (11.8) |
| HCV+ | 37 (14.6) | 2 (1.6) | 39 (10.3) | 120 (4.2) | 13 (1.6) | 133 (3.9) |
| HIV+ | 15 (6.5) | 2 (1.6) | 17 (4.8) | 0.038 | 26 (1.0) | 36 (1.1) |
| BMI | | | | | | |
| Normal | 100 (52.1) | 55 (52.4) | 155 (52.2) | 986 | 943 (41.5) | 1315 (45.8) |
| Overweight | 71 (37.0) | 38 (36.2) | 109 (36.7) | 1000 (44.0) | 372 (62.0) | 1374 (40.9) |
| Obese | 21 (10.9) | 12 (11.4) | 33 (11.1) | 330 (14.5) | 54 (9.9) | 384 (13.4) |
| Steatosis* | 12 (44.4) | 7 (77.8) | 19 (52.8) | 0.128 | 56 (46.7) | 62 (45.3) |
| Hypertension | 62 (22.0) | 9 (6.3) | 71 (16.7) | <0.001 | 750 (24.8) | 57 (6.6) |
| Diabetes | 27 (9.6) | 3 (2.1) | 30 (7.1) | 0.005 | 346 (11.5) | 36 (4.2) |
| Other comorbidities | 102 (36.2) | 52 (36.6) | 154 (36.3) | 0.928 | 1545 (51.2) | 224 (26.0) |
| Number of comorbidities | | | | | | |
| 0 | 138 (48.9) | 84 (59.2) | 222 (52.4) | 0.091 | 1165 (38.6) | 597 (69.2) |
| 1 | 87 (30.8) | 37 (30.8) | 124 (29.2) | | 889 (29.4) | 182 (21.1) |
| 2 | 35 (12.4) | 17 (12.0) | 52 (12.0) | | 567 (18.8) | 64 (7.4) |
| >2 | 22 (7.8) | 4 (2.8) | 26 (6.1) | | 398 (13.2) | 20 (2.3) |

Table 2. Liver disease progression cofactors and comorbidities in HBV/HDV coinfecting and HBV mono-infected patients. * Missing steatosis in 3773 (87%). ** p value Chi-square test

| Comorbidities | HBV/HDV coinfecting patients | | | p* |
|-----------------|-----------------------------------|--------------------------------------|-----------------|--------|
| | Patients with cirrhosis N=296 (%) | Patients without cirrhosis N=128 (%) | Total N=424 (%) | |
| Autoimmune | 10 (3.4) | 3 (2.3) | 13 (3.1) | 0.762 |
| Cardiovascular | 69 (23.3) | 19 (14.8) | 88 (20.7) | 0.048 |
| Cerebrovascular | 2 (0.7) | 0 (0.0) | 2 (0.5) | >0.999 |
| Diabetes | 23 (7.8) | 7 (5.5) | 30 (7.1) | 0.396 |
| Dyslipidemia | 5 (1.7) | 7 (5.5) | 12 (2.8) | 0.031 |
| Haematological | 19 (6.4) | 4 (3.1) | 23 (5.4) | 0.169 |
| Endocrine | 8 (2.7) | 4 (3.1) | 12 (2.8) | 0.759 |
| Neurological | 7 (2.4) | 5 (3.9) | 12 (2.8) | 0.359 |
| Psychiatric | 8 (2.7) | 5 (3.9) | 13 (3.1) | 0.544 |
| Renal | 16 (15.4) | 5 (3.9) | 21 (4.9) | 0.514 |
| Respiratory | 6 (2.0) | 6 (4.7) | 12 (2.8) | 0.198 |
| Digestive | 46 (15.5) | 5 (3.9) | 51 (12.0) | 0.001 |
| Dermatologic | 3 (1.0) | 3 (2.3) | 6 (1.4) | 0.372 |
| Tumors | 14 (4.7) | 7 (5.5) | 21 (5.0) | 0.747 |

Table 3. Comorbidities distribution in enrolled patients with chronic HDV infection according to the cirrhosis stage. * p value Chi-square test