

PERIPHERAL HCV-SPECIFIC CYTOTOXIC RESPONSE DETECTION AT WEEK 12 OF PEGYLATED-INTERFERON ALFA-2 β PLUS RIBAVIRIN TREATMENT FOR CHRONIC HCV INFECTION CORRELATES WITH SUSTAINED VIROLOGIC RESPONSE DEVELOPMENT.

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BACKGROUND AND AIMS

The second phase of viral load (VL) decay, during Peg-interferon (IFN) plus ribavirin (RBV) treatment for hepatitis C virus (HCV) infection, is probably due to specific immune response. Low HCV VL decrease at week 12 (w12) of treatment has 100% negative predictive value of sustained virologic response (SVR), and this could be related with the absence of HCV-specific cytotoxic T lymphocytes (CTL). The development of SVR after Peg-IFN α 2b plus RBV treatment according to the detection of HCV-specific CTL response at w12 was analysed.

METHODS

A longitudinal cohort study was carried out. 25 HLA-A2+ chronic HCV patients were recruited. Peripheral blood lymphocytes (PBL) were taken at weeks 0 and 12 of treatment. HCV-specific CTL response was tested directly ex-vivo and after specific in-vitro stimulation. HCV-specific CTLs were detected by PBL staining with anti-CD8-Cy5 mAb plus HLA-A2/peptide-PE multimers against two NS3 epitopes and subsequent flow-cytometric analysis. Samples were split into two groups according to the presence of detectable HCV-specific CTLs at w12 (Group 1: detection, Group 2: no detection). SVR rate was compared between both groups and ROC analysis of the ability of w12 HCV-specific CTL detection to predict SVR was carried out.3

RESULTS

Both groups were similar according to sex, age, basal viral load, HCV-genotype and liver fibrosis. Group 1 and 2 consisted of 14 and 36 samples respectively. SVR was higher in group 1 (93%) than in group 2 (47%) ($p=0.003$) (Fig.1). In genotype-1 patients, an increase on HCV-specific CTL frequency between base line and w12 of treatment was observed ($p=0.011$), but not in group 2 (Fig.2). Also HCV-specific CTL proliferation was more frequent in group 1 than in group 2 during treatment ($p=0.025$) (Fig.3). Detection of HCV-specific CTLs at w12 correlated with the level of HCV viral load decrease between base line and w12 ($p=0.016$, $r=0.389$) (Fig.4). The detection of HCV-specific CTLs at w12 among HCV genotype-1 patients with early virologic response (EVR) had a 100% PPV of SVR (Fig.5).

CONCLUSIONS

Detection of HCV-specific CTLs at w12 of Peg-IFN α 2b+RBV treatment correlates with the development of SVR. Interestingly, in EVR genotype-1 cases, this fact predicts accurately the development of SVR.

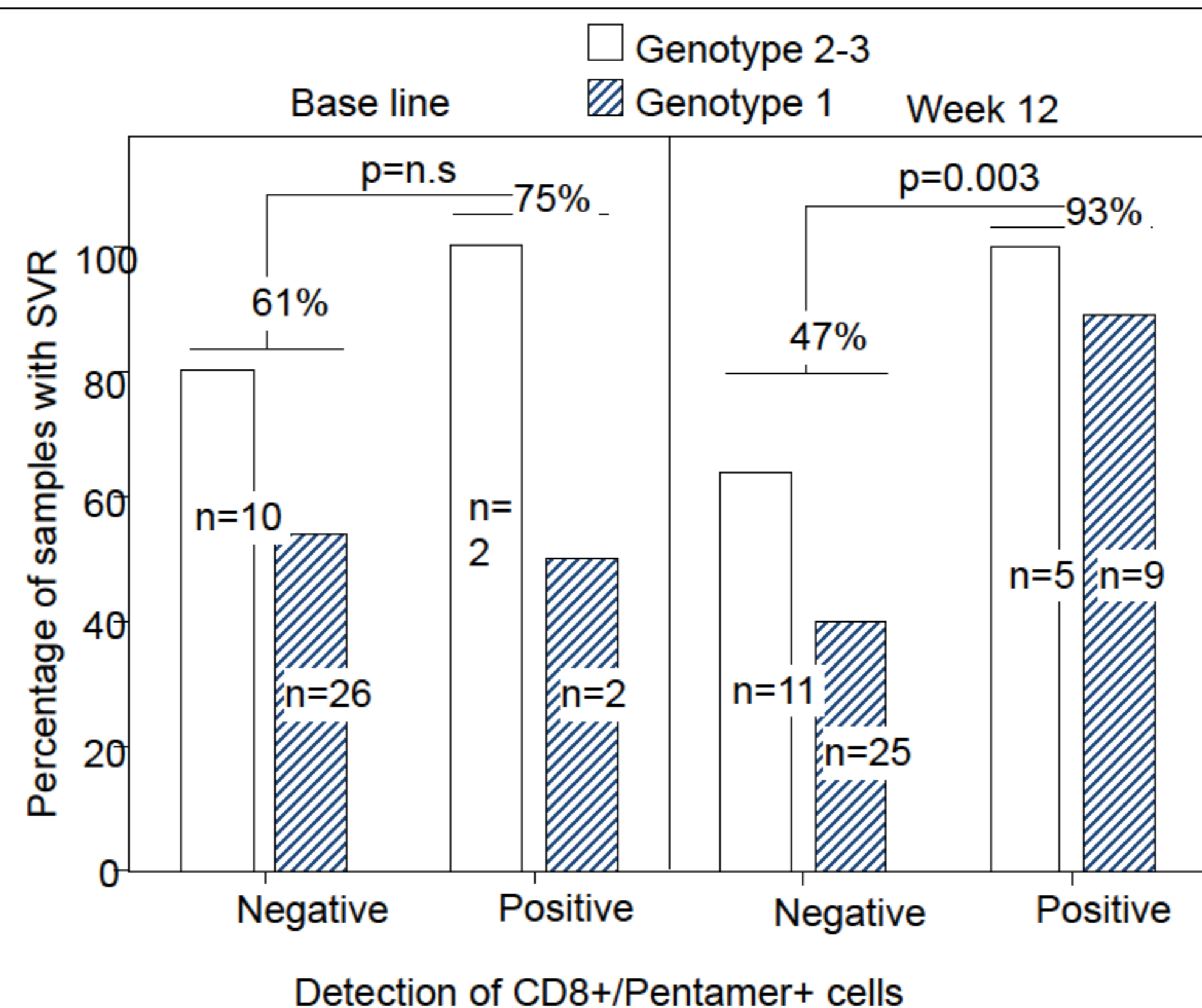


Fig 1. Bar graph showing the SVR rate in relation to pentamer+/CD8+ cell detection at w0 and w12 of treatment; According to the presence of HCV-specific CTLs at w12 of treatment are displayed. n: number of sample, n.s: non significant.

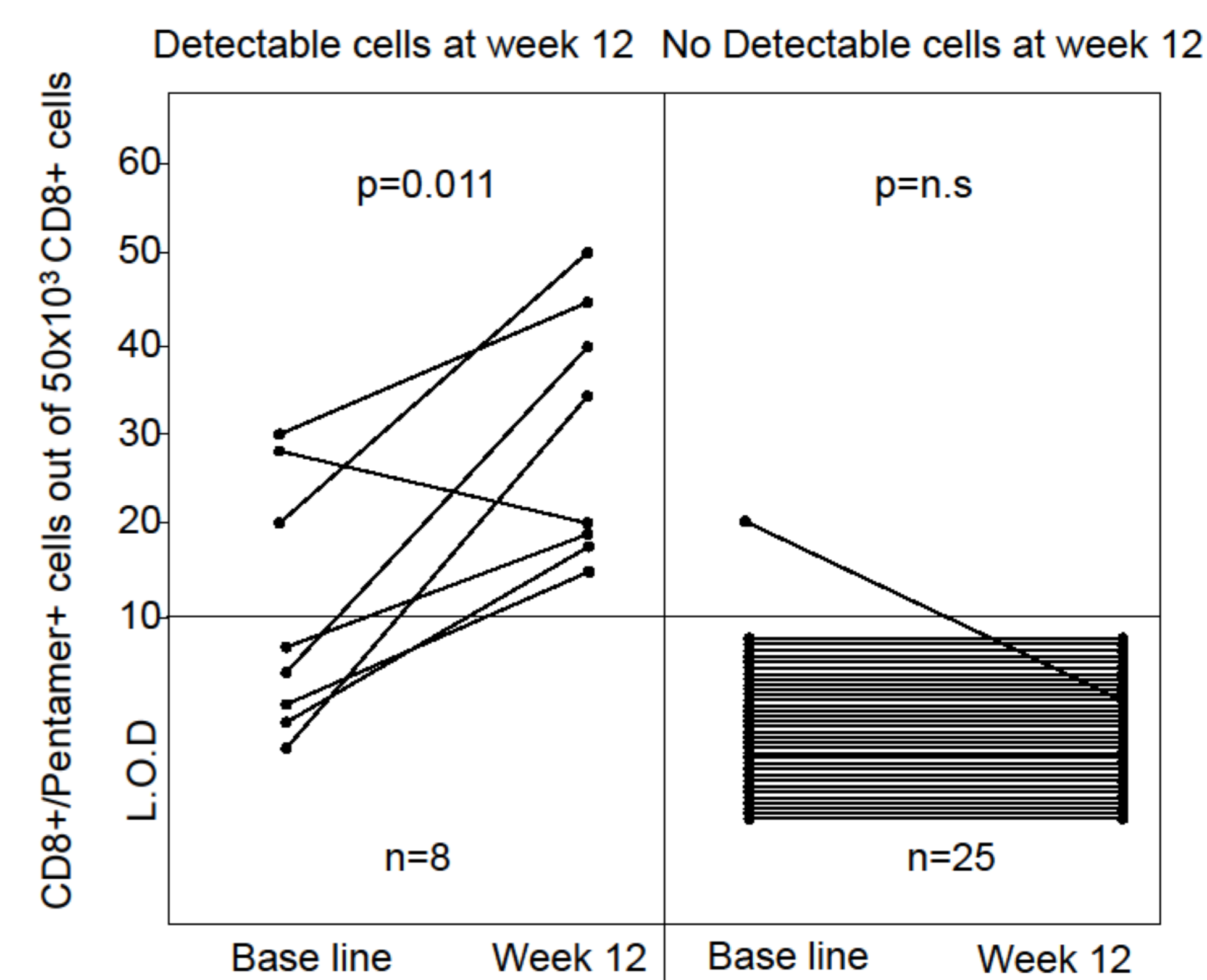


Fig 2. Scatter plot showing the dynamics of pentamer+/CD8+ cells between base-line and w12. n: number of sample, n.s: non significant.

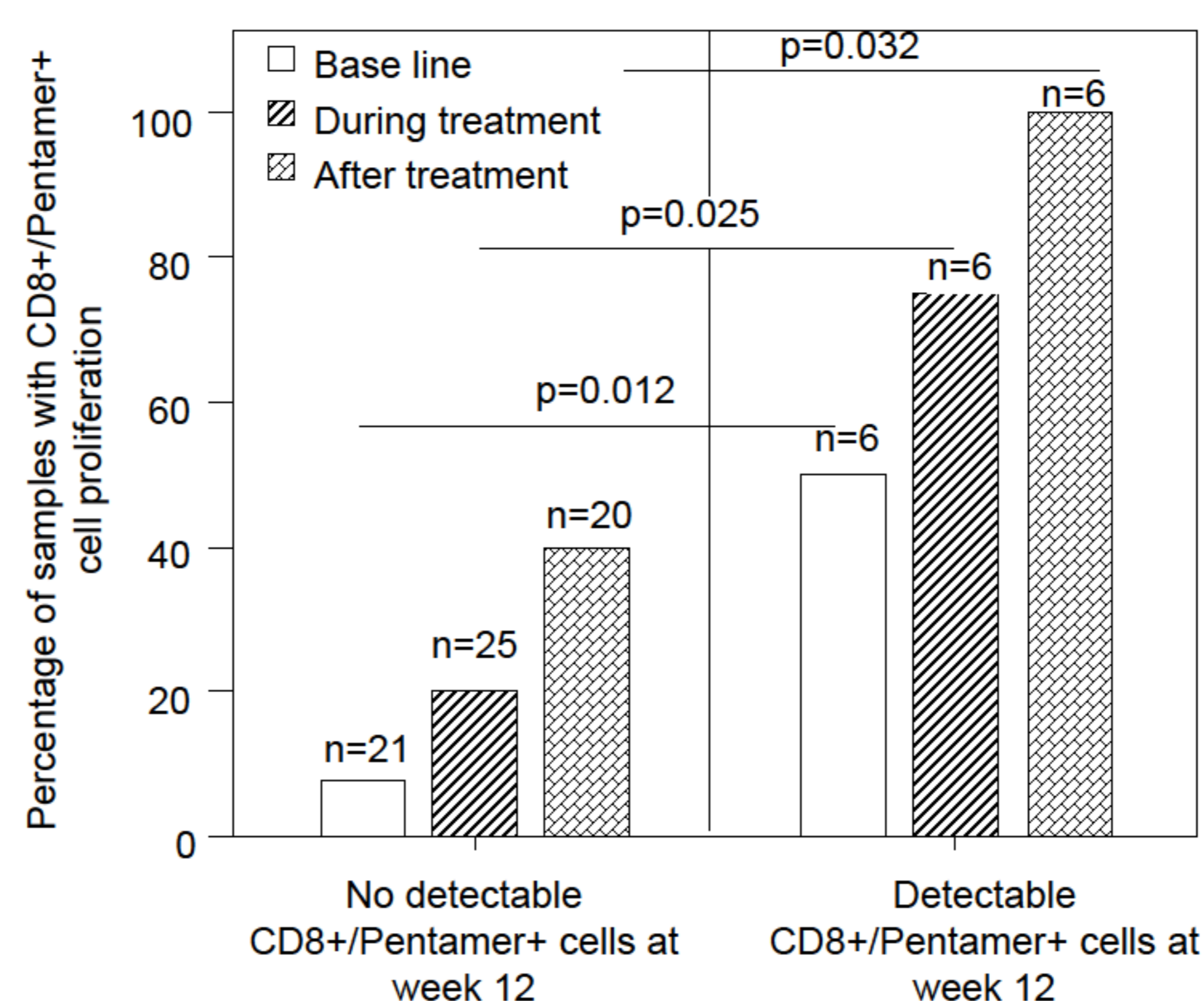


Fig 3. The frequency of cases with specific proliferation during treatment and follow-up. n: number of sample, n.s: non significant.

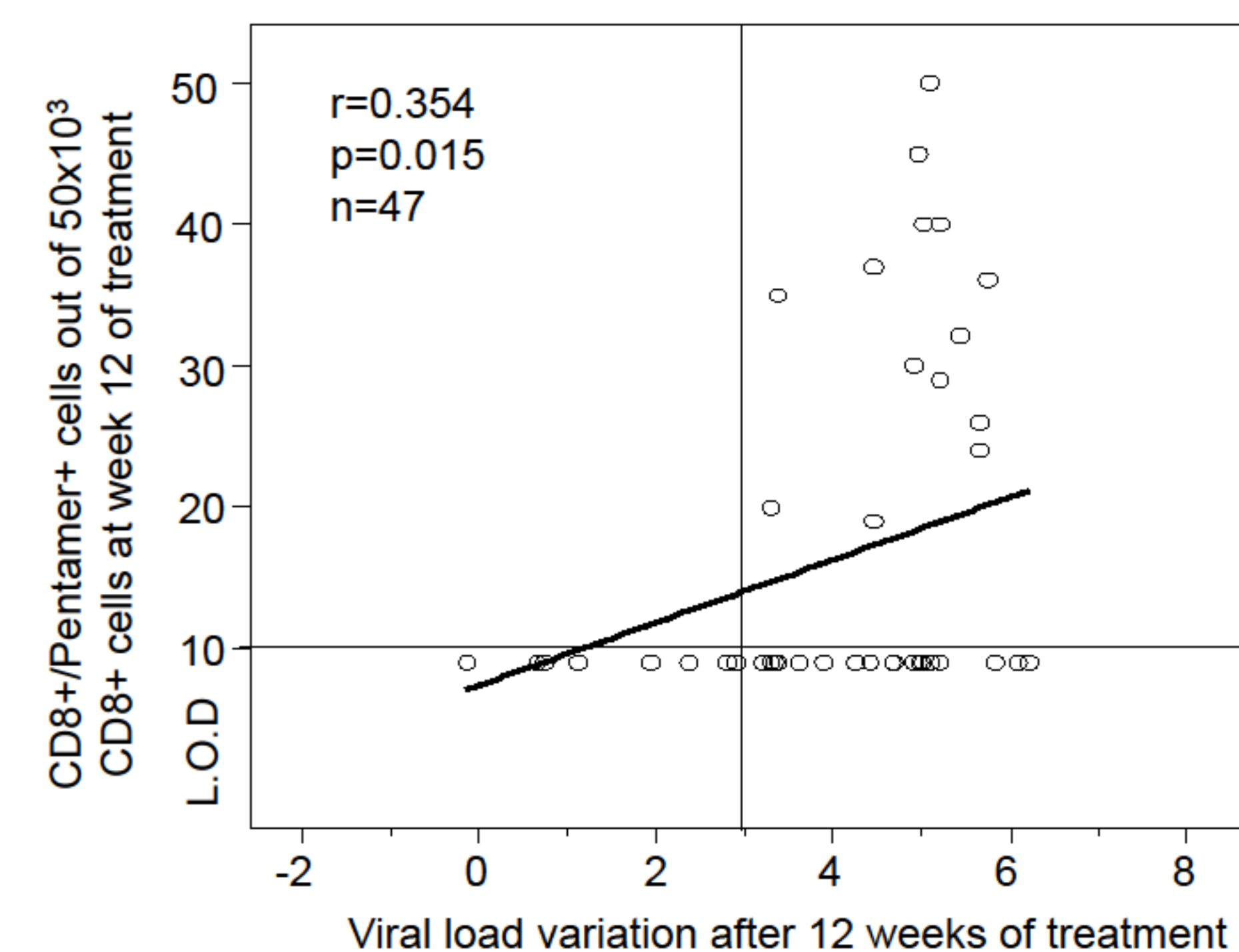


Fig 4. Scatter-plot showing a positive correlation between HCV viral load variation after first 12 weeks of treatment and pentamer+/CD8+ cell detection at w12 of treatment. n: number of samples, n.s: non significant, L.O.D: limit of detection, *Mann-Whitney U test, §Spearman's correlation coefficient.

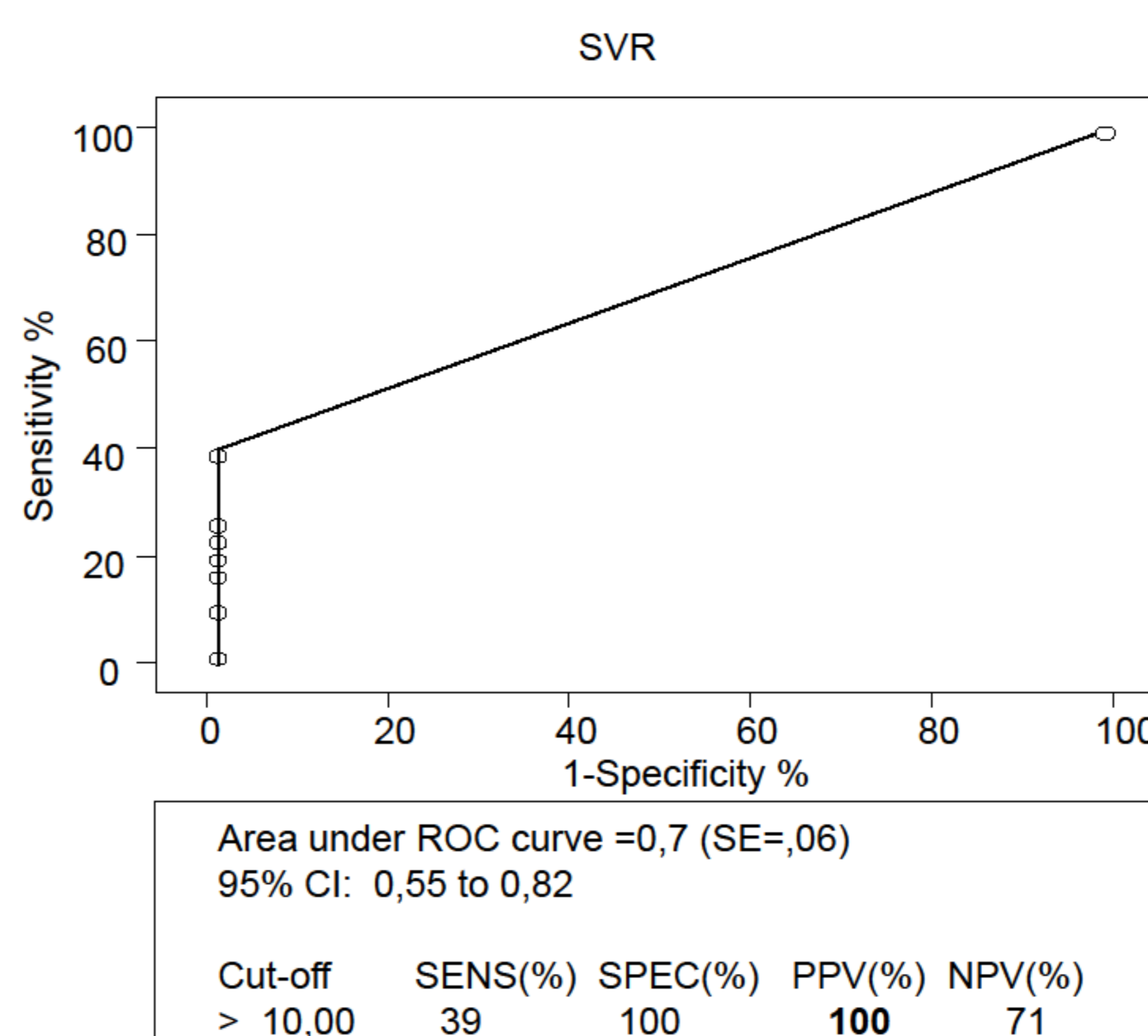


Fig 5. ROC analysis of the ability of "detectable pentamer+/CD8+ cells at w12" to predict SVR among chronic hepatitis C genotype-1 patients with early or delayed virologic response (EDVR): (A) ROC curve showing the ability of "HCV-specific CTL detection at w12 of treatment" to predict SVR among EDVR genotype-1 chronic hepatitis C patients. (B) Scatter-plot showing pentamer+/CD8+ cell frequency at w12 of treatment in EDVR genotype-1 chronic hepatitis C patients according to SVR outcome. Black lines: mean value. SVR: sustained virologic response, ROC: receiver operating characteristics curve, PPV: positive predictive value, NPV: negative predictive value, L.O.D.: limit of detection, *Mann-Whitney U test.