response (VR) (defined as undetectable serum HDV RNA) and only 23% achieved a complete virological response (CVR) (defined as the combination of undetectable HDV RNA and loss of HBsAg and anti-HBsAg seroconversion in serum).[2]

While we agree that one of the limitations of this study is the small sample size, and that definitive conclusions cannot be drawn, the overall long-term experience is still useful for clinicians attempting to help their HDV patients, given the paucity of available therapies. Since the initial publication, one additional patient in this cohort has achieved a CVR after 606 weeks of therapy.

We greatly appreciate the single experience reported by Maraolo *et al.*, describing a patient that achieved a CVR after 245 weeks of therapy. While this expands on published data that CVR is possible with long-term peginterferon therapy, it should be noted that CVR has been reported with interferon-based therapy out to 12 years.[3]

Thus, given the poor response rates, long-term risks of interferon-based therapies, and the uncertainty of long-term therapy coupled with cost/benefit, the need for better therapies in HDV is clear. However, there may be light at the end of the tunnel, as novel therapeutic compounds such as prenylation inhibition and viral entry inhibition in HDV appear promising.[4–6]

Despite general consensus that HDV is the most severe form of viral hepatitis, therapies for this dreadful disease are still in their infancy.[7] Where we are today with HDV is reminiscent of the early days of hepatitis C therapy with similar abysmal response rates. Thus, we agree with Maraolo *et al.*, that while long-term peginterferon therapy should not be completely excluded, we should continue the search for better therapies for our patients in this rapidly progressive disease.

AUTHORSHIP

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Letter: prognostic scoring systems for hepatocellular carcinoma patients – the jury is still out

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Sirs, We read with great interest the article by Pinato *et al.*, where the normalisation of inflammation-based-index (IBI) score after trans-arterial chemoembolisation (TACE) was shown to be an independent predictor of survival in hepatocellular carcinoma (HCC) patients.[1]

In the last years, a number of scores and nomograms have been proposed but, unfortunately, none of them has been unequivocally confirmed in clinical practice.[2, 3] All these efforts, often properly conducted, suffered from a well-known statistical phenomenon called 'overfitting'. Overfitting occurs when a model maximises its performance in one set of data, but its predictive value is not confirmed elsewhere due to random fluctuations of patient characteristics in different clinical and demographical backgrounds. The routinely performed external validation doesn't seem to correctly overcome this problem. The very fact indeed that so

many different scores keep on being proposed confirms and gives proof of the aforementioned concept.

Moreover, another methodological concern may be raised by reading the article by Pinato *et al.*, as the dynamic evolution of the score doesn't seem to be properly captured. In fact, the simple comparison between patients who experienced the normalisation of IBI and those without any modification of the score is biased in favour of the former group, as patients who eventually become responders must have survived long enough to have their score assessed. No such 'guarantee time' is required for the latter group. Thus, patients with poorer survival will not have the opportunity to enter the responder group and this may lead to a bias in the comparison of the outcomes. This is why more appropriate statistical tools are needed, such as Landmark or Mantel-Byar analysis.[4]

In conclusion, no point-score model seems to provide a universal and largely applicable tool to guide the therapeutic algorithm in HCC patients.

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Letter: *Helicobacter*-negative gastritis – a distinct condition?

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Sirs, We read with great interest the article by Genta and Sonnenberg,[1] which represents a milestone in the pathological definition of non-*Helicobacter* gastritis. However, a question arises about the term non-*Helicobacter*. Does it mean the absence of *H. pylori* or does the definition need to be extended to other *Helicobacter* species? Despite this, we fully agree that this condition may reflect an autonomous entity, with its own peculiar epidemiologic characteristics and different evolution during follow-up, and would like to emphasise that an exhaustive diagnostic work-up is needed for such a condition.

First, we agree that 'missed germs' represent only a small proportion of *Helicobacter*-negative gastritis (only the 7.4% of the impressive authors' series showed *Helicobacter* misdiagnosis at a second biopsy sampling after 18 months). Indeed, in a recent study of our group, histology failed to detect the bacterium in 6.3% of cases, while DNA *Helicobacter* sequences in gastric tissue and urea breath/antigen stool test unmasked the infection.[2] However, since the stomach is not considered as a 'sanctuary' for bacteria, other species composing the gastric microbiota could be involved.[3] The stomach indeed can harbour *Streptococcus* and *Prevotella* which, surprisingly, may account for up to 40% of gastric diseases in non-*H. pylori* infected subjects.[4] Finally, the problem of other *Helicobacter* species, especially *H. heilmannii*, showing peculiar histological and immunohistochemical traits,[5] remains unclear.

Second, the authors demonstrated that a small amount (3.5%) of gastritis may be related to inflammatory bowel disease. For this reason, other autoimmune disorders must be considered: coeliac disease, for instance, can induce a microscopic pattern that could be indistinguishable from *H. pylori* infection in a minority of cases.[6] Furthermore, a picture of gastritis as an epiphenomenon of rheumatologic diseases could be considered, similar to the well-documented associated gastro-oesophageal motility disorders.

Finally, nonsteroidal anti-inflammatory drugs may cause chronic gastritis in up to 9% of patients in the absence of *Helicobacter*.[7] Additionally, other medications (steroids, bisphosphonates, anti-coagulants, anti-depressants) have also been associated with *Helicobacter*-negative gastritis, and chronic use of proton pump inhibitor