



Beyond replacing endoscopy: portal hypertension assessment by AI in unresectable HCC

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Unresectable hepatocellular carcinoma (HCC) is rarely an isolated oncologic condition. In patients with cirrhosis, tumor control and hepatic reserve are inextricably intertwined, with portal hypertension (PH) potentially shaping both the safe delivery of systemic therapy and the magnitude of its clinical benefit. This is particularly relevant in patients treated with atezolizumab-bevacizumab (AtezoBev), as hepatic decompensation has emerged as a major determinant of mortality, sometimes outweighing tumor progression itself^[1]. Against this background, Rabasco Meneghetti *et al.* asked whether information already contained in routine contrast-enhanced computed tomography (CT) could replace part of the endoscopic work-up, particularly pretreatment esophagogastroduodenoscopy (EGD) and provide information on the eventual appearance of hepatic decompensation and on prognosis^[2]. Their multicenter retrospective study included 489 patients with cirrhosis and unresectable HCC treated with AtezoBev at five French centers. Arterial-phase CT was available for 341 patients and processed using the frozen vision encoder of MERLIN, a pretrained three-dimensional vision-language foundation model designed to extract generalizable features from volumetric CT images for a wide range of clinical tasks^[3]. Finally, the authors developed the HepatoSageCT score and analyzed its ability to predict the presence of esophageal varices (EVs) and the appearance of hepatic decompensation^[2]. Portosystemic shunts (PSS), manually identified by a radiologist, emerged as the strongest non-invasive predictor of EVs^[2]. Moreover, the HepatoSageCT score provided incremental predictive value beyond PSS alone, improving risk stratification for EVs while also enabling prognostic assessment of hepatic decompensation^[2]. In the validation pathway population, comprising 125 patients without prior acute variceal bleeding, PSS combined with HepatoSageCT yielded a negative predictive value (NPV) of 87.5% for any-grade EVs, potentially sparing EGD in 24/125 patients. Three of 72 patients with EVs were missed (4.2%), all with grade 1 varices^[2].



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The architecture of the study is clinically persuasive: an interpretable radiological sign provides the first layer, and artificial intelligence (AI) refines the uncertainties in the PSS-negative group. It also extracts additional value from imaging already required for HCC staging, without adding further procedures to the patient's burden. Notably, a foundation-model approach reduces dependence on very large, HCC-specific annotated imaging datasets. The inclusion of patients across a broad spectrum of liver disease severity reflects real-world clinical practice, while the consistent findings observed in patients with compensated disease are particularly relevant, as these patients are likely to derive the greatest clinical benefit from safely deferring pretreatment EGD.

AI-based risk stratification in immunotherapy-treated HCC is not unprecedented. Models combining CT and clinical data have predicted overall survival with anti-PD-1 therapy, while pretreatment radiomics has predicted response, overall survival and progression-free survival after AtezoBev^[4,5]. Prognosis alone rarely identifies a superior alternative regimen, while HepatoSageCT^[2] targets a potentially modifiable competing risk. In compensated, non-selective beta-blockers (NSBBs)-naïve patients, a PSS/HepatoSageCT score suggestive of EVs could prompt EGD and particularly NSBB initiation once clinically significant portal hypertension (CSPH) is confirmed. Conversely, the absence of PSS combined with a low score may identify patients in whom EGD could potentially be safely deferred or even avoided, pending prospective validation. This creates a plausible route from prediction to intervention.

The clinical significance of reproducing an endoscopic diagnosis warrants a more nuanced interpretation. Baveno VII shifted the therapeutic target from variceal size to CSPH, recommending NSBBs, particularly carvedilol, to prevent the first decompensation^[6]. This disease-modifying concept is supported by the trial of β blockers to prevent decompensation of cirrhosis in patients with CSPH (PREDESCI), which demonstrated that NSBBs can delay decompensation in patients with compensated cirrhosis and CSPH^[7]. Thus, among patients who already meet criteria for NSBB therapy, identifying EVs may add little to clinical decision-making. Conversely, evaluating CSPH in advanced HCC remains challenging: tumor-related vascular changes may weaken conventional algorithms based on liver stiffness and platelet count. In addition, hemodynamic assessment is invasive and may not capture every component of PH^[8,9]. However, according to Baveno VIII^[10], this limitation appears to apply primarily to patients with macrovascular invasion, in whom non-invasive tests (NITs) for CSPH and high-risk varices may not be applicable. Nonetheless, in patients with compensated advanced chronic liver disease and Barcelona Clinic Liver Cancer (BCLC) stages 0-C without macrovascular invasion, liver stiffness ≤ 15 kPa combined with a platelet count $\geq 150 \times 10^9/L$ can rule out CSPH with an NPV $> 90\%$. EGD may therefore be avoided in this setting^[10,11]. It should be considered that, despite a 94% agreement, the corresponding statement received only a weak recommendation from the consensus, reflecting the conflicting evidence available in the literature^[9] and underscoring the need for confirmatory studies to determine the clinical impact of safely deferring or avoiding EGD. This Baveno-based recommendation is distinct from the proposed CT/AI pathway, for which EGD deferral requires prospective validation. EGD remains the reference standard in selected clinical settings. CT cannot identify red wale markings or other endoscopic high-risk stigmata, nor can it reliably grade varices. In secondary prophylaxis, endoscopic variceal ligation combined with NSBBs remains standard, and, importantly, patients with previous acute variceal bleeding were excluded from the EV decision-making workflow^[2]. The proposed pathway is therefore most credible as a primary-prophylaxis triage or when access to timely EGD is limited. The absence of missed large EVs in the validation cohort does not necessarily imply that no varices needing treatment were missed. Nevertheless, this finding is somewhat reassuring, particularly in a real-world setting characterized by heterogeneous and relatively limited use of NSBBs. Of note, the same treatment pattern extended to patients with previous or current hepatic decompensation. Although such variability in NSBBs use may have influenced variceal burden and bleeding risk, the consistent performance of this approach under these conditions strengthens its relevance to routine clinical practice.

Several methodological points should be considered to better interpret the relevance of these findings. Held-out validation and leave-one-center-out testing are evident strengths of the study. On the other hand, this retrospective study was restricted to French centers, included a large majority of males (87%), and suitable arterial-phase CT was available for about 70% of the cohort. No hemodynamic data were available, and EVs were used as a pragmatic surrogate for CSPH. Although CSPH is the main driver of EVs, these are not invariably present in patients with CSPH, with studies suggesting that they develop in only a proportion of patients, particularly in the compensated stage of cirrhosis^[12]. Moreover, PSS were manually identified and treated equally regardless of number, dimension or anatomy. Combining compensated, previously decompensated and currently decompensated patients enhanced real-world representation but led to analyzing together very diverse groups of patients, particularly regarding prognostic and functional stratification. Of note, addition of clinical data did not improve the ability of the HepatoSageCT score to predict decompensation consistent with the relevant role of ascites and splenomegaly, both readily detectable on imaging^[2]. Data obtained in compensated patients are particularly interesting. In this group of patients, AI detects subtler imaging manifestations of PH, predicting both baseline EVs and subsequent hepatic decompensation^[2].

The two outputs of the study represent different clinical expressions of the same underlying PH phenotype, although their actionability differs. The EVs pathway may be particularly valuable in compensated, NSBBs-naïve patients for whom non-invasive assessment of CSPH is less reliable, especially those with macrovascular invasion and/or large tumors extensively involving the right hepatic lobe. In contrast, the decompensation score retains prognostic value, stratifying patients according to risk but without validated thresholds to inform intensified monitoring, deferment of bevacizumab, or selection of an alternative treatment regimen. However, in the study by Rabasco Meneghetti *et al.*, all patients received AtezoBev, and any potential benefits from alternative treatments cannot be inferred in the absence of a treatment-outcome interaction analysis^[2]. Moreover, the exploratory NSBBs analysis is vulnerable to confounding by indication, and association with overall survival does not show that AI-guided management improves survival. These scores should inform, rather than dictate, treatment decisions and should not, in isolation, preclude otherwise appropriate therapy.

This field is of considerable interest and has been the focus of substantial research efforts. Kramer *et al.* recently reported the results of an international, multi-cohort study validating the Cirrhosis Risk Identifier (CIRI), a machine-learning model based on laboratory and demographic data that predicts first hepatic decompensation in patients with compensated advanced chronic liver disease with an accuracy comparable to that of hepatic venous pressure gradient measurement and greater precision than widely used NITs^[13]. The advent of AI will provide a powerful tool to fine-tune the management of these complex patients. In the meantime, clinicians may immediately value the results provided by detection of PSS as good predictors of PH.

In prospect, the great opportunity is not simply to reduce endoscopic workload, but to move PH assessment upstream in the HCC pathway, from identifying existing EVs to anticipating hepatic decompensation. Future prospective studies should predefine safety-oriented thresholds, quantify calibration and net benefit, automate PSS characterization, and prioritize patient-centered outcomes, including missed large or high-risk EVs, actual EGD avoided, time to systemic treatment, bleeding, first or further decompensation and survival^[14,15]. Ultimately, success should not be measured by a higher area under the receiver operating characteristic curve (AUROC), but by earlier disease-modifying treatments, safer oncologic decisions and fewer episodes of hepatic decompensation.

DECLARATIONS

Authors' contributions

Conceptualization: Voza A, Vizzutti F, Marra F

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Marra F is a consultant for Roche, AstraZeneca, MSD, and Ipsen. The other authors declare no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

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Not applicable.

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