Hepatocellular Cancer Surveillance in Patients with Advanced Chronic Liver Disease

Gu W, de Lédinghen V, Aubé C, et al. Hepatocellular Cancer Surveillance in Patients with Advanced Chronic Liver Disease. *NEJM Evid*. 2024;3(11):EVIDoa2400062.
doi:10.1056/EVIDoa2400062

Abstract

Background: Patients with advanced chronic liver disease (ACLD) are at high risk of developing hepatocellular carcinoma (HCC). Therefore, biannual surveillance is recommended. This large-scale multicenter study aimed to stratify the risk of HCC development in ACLD.

Methods: From 3016 patients with ACLD screened in 17 European and Chinese centers, 2340 patients with liver stiffness measurement (LSM) determined using different techniques (two-dimensional shear-wave elastography [2D-SWE], transient elastography, and point shear-wave elastography) and with different disease severities were included. Cox regression was used to explore risk factors for HCC. We used these data to create an algorithm, named PLEASE, but referred to in this manuscript as "the algorithm"; the algorithm was validated in internal and two external cohorts across elastography techniques.

Results: HCC developed in 127 (5.4%) patients during follow-up. LSM by 2D-SWE (hazard ratio: 2.28) was found to be associated with developing HCC, alongside age, sex, etiology, and platelet count (C-index: 0.8428). We thus established the algorithm with applicable cutoffs, assigning a maximum of six points: platelet count less than 150×10^9/l, LSM greater than or equal to 15 kPa, age greater than or equal to 50 years, male sex, controlled/uncontrolled viral hepatitis, or presence of steatotic liver diseases. Within 2 years, with a median follow-up of 13.7 months, patients in the high-risk group (≥4 points) had an HCC incidence of 15.6% (95% confidence interval [CI], 12.1% to 18.7%) compared with the low-risk group, at 1.7% (95% CI, 0.9% to 2.5%).

Conclusions: Our algorithm stratified patients into two groups: those at higher risk of developing HCC and those at lower risk. Our data provide equipoise to test the prospective utility of the algorithm with respect to clinical decisions about screening patients with ACLD for incident HCC. (Funded by the German Research Foundation and others; ClinicalTrials.gov number, NCT03389152.).

Σχόλιο

- Στη μελέτη αυτή χρησιμοποιήθηκε ένα μοντέλο πρόβλεψης του κινδύνου εμφάνισης ηπατοκυτταρικού καρκίνου (HKK) σε ασθενείς με προχωρημένη χρόνια ηπατικής νόσο (ACLD), όπως αυτή ορίσθηκε με την ταξινόμηση του BAVENO VII. Ο στόχος ήταν η κατάταξη των ασθενών σε αυτούς, που ήταν υψηλού κινδύνου και σε όσους αντίθετα ήταν χαμηλού κινδύνου για την εμφάνιση HKK.
- Το μοντέλο ονομάσθηκε PLEASE score (**PL**atelets, **E**lastography, **A**ge, **S**ex, **E**tiologies) από τα αρχικά των παραμέτρων, που χρησιμοποιήθηκαν για τον σχεδιασμό του. Ασθενείς, που έλαβαν 4 πόντους και άνω ήταν υψηλού κινδύνου για την εμφάνιση HKK, ενώ ασθενείς, που έλαβαν κάτω από 4 ήταν χαμηλού κινδύνου για την εμφάνιση HKK.
- Η μελέτη συμπεριέλαβε συνολικά περίπου 3.000 ασθενείς και είχε έναν πληθυσμό μελέτης και δύο πληθυσμών επιβεβαίωσης των αποτελεσμάτων από συνολικά 17 κέντρα της Ευρώπης και της Κίνας.
- Το διάμεσο διάστημα παρακολούθησης ήταν 13.7 μήνες.
- Το 42% των ασθενών είχαν στεατωτική νόσο του ήπατος (SLD). Οι ασθενείς με υψηλό κίνδυνο, βάσει του PLEASE score, εμφάνισαν ετήσιο κίνδυνο HKK περίπου 15%, ενώ οι ασθενείς με χαμηλό κίνδυνο είχαν ετήσιο κίνδυνο περί το 1.7%. Τα ποσοστά αυτά παρέμεναν παρόμοια και για τις δύο ομάδες κινδύνου ακόμη και όταν οι ασθενείς μελετήθηκαν ξεχωριστά ανάλογα με την αιτιολογία της ηπατοπάθειας (στεατωτική νόσος ή ιογενής ηπατίτιδα).
- Η μελέτη αυτή είναι η πρώτη, που σε ευρεία κλίμακα προτείνει έναν αλγόριθμο πρόβλεψης του κινδύνου για HKK σε ασθενείς με ACLD, ενώ αφορά εξίσου σε ασθενείς με ιογενή και μη ιογενή ηπατική νόσο.

- Επιπλέον, προτείνει την αξιολόγηση των ασθενών ως και 4 φορές ετησίως με το PLEASE score για ασθενείς υψηλού κινδύνου, ενώ αντίθετα προτείνει ετήσια αξιολόγηση με το PLEASE score για ασθενείς με χαμηλό κίνδυνο ΗΚΚ.
- Σύμφωνα με τους ερευνητές, η εφαρμογή του νέου αλγόριθμου, είχε καλύτερη σχέση κόστους-οφέλους συγκριτικά με τη συνήθη μέθοδο επιτήρησης με υπερηχογράφημα κοιλίας και α-φετοπρωτεΐνη ανά 6μηνο στην ομάδα των ασθενών με χαμηλό κίνδυνο για ΗΚΚ.
- Το PLEASE score θα μπορούσε να αποτελέσει ένα νέο αλγόριθμο επιτήρησης για ΗΚΚ, ωστόσο χρήζει περαιτέρω επαλήθευσης σε προοπτικό επίπεδο (η παρούσα μελέτη ήταν αναδρομική).

Ακολουθούν σημαντικές εικόνες από τη μελέτη.

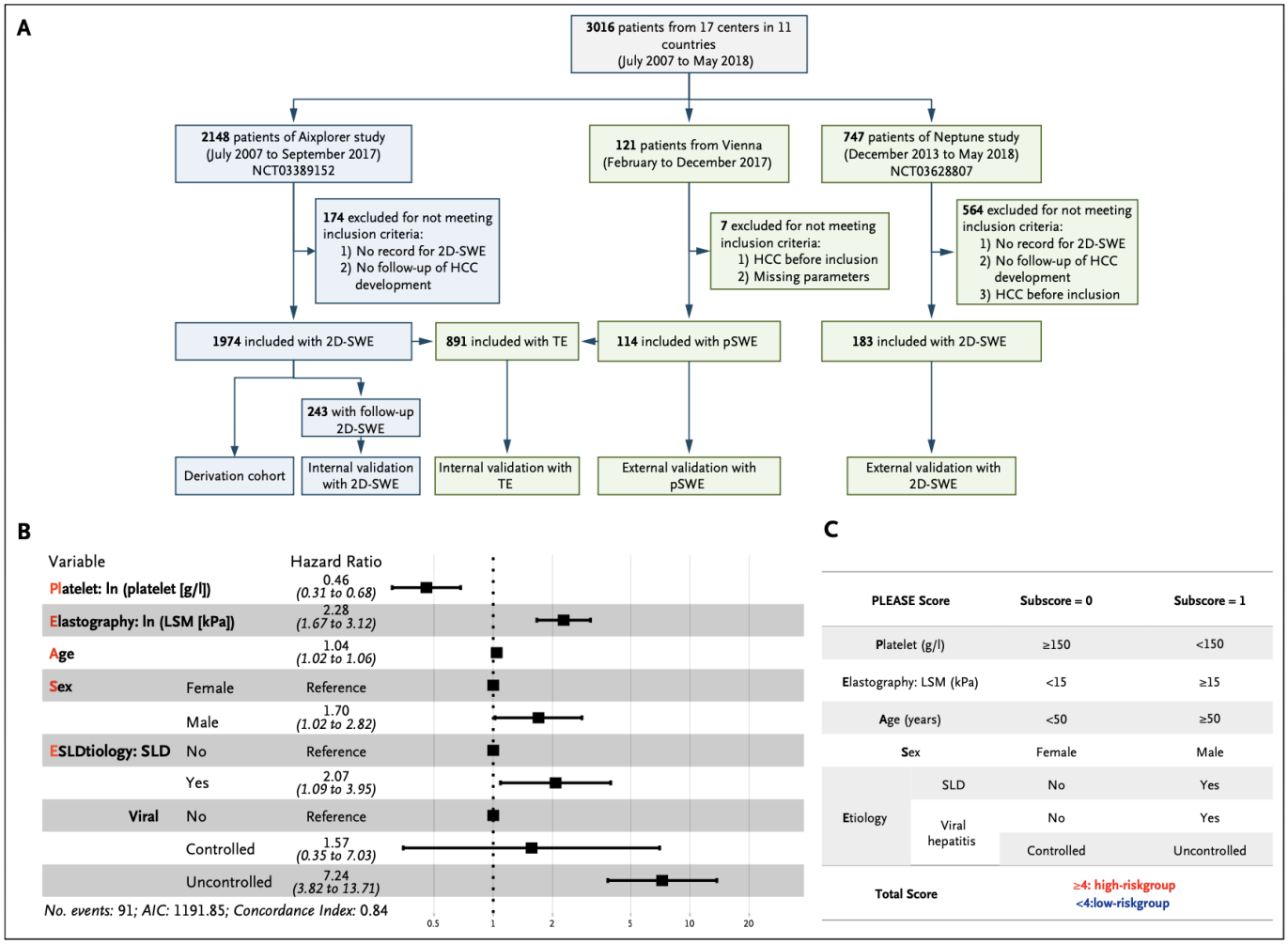


Figure 1. Flowchart and Model Development.

Panel A: study flowchart including derivation cohorts (blue shading) and validation cohorts (green shading) from July 2007 to May 2018. Panel B: forest plot of hazard ratios of all independent risk factors of de novo HCC development within 2 years using a Cox regression model. Panel C: our algorithm's score and subscore for each variable based on Youden index and Cox regression results; values shown as "=0" represent the specified cutoff for a score of zero in the final PLEASE score, while values differing from this cutoff were scored as "1." 2D-SWE denotes two-dimensional shear-wave elastography; AIC, Akaike information criterion; g, gram; HCC, hepatocellular carcinoma; kPa, kilopascal; l, liter; ln, natural logarithm; LSM, liver stiffness measurement; OR, odds ratio; PLEASE, platelet, elastography, age, sex, and etiologies algorithm; pSWE, point shear-wave elastography; SLD, steatotic liver disease; and TE, transient elastography.

Table 1. General Characteristics of the Derivation Cohort of the Aixplorer Study and Comparison between Patients with and without Hepatocellular Carcinoma Development during Follow-up.*

Variable†	Aixplorer Study (n=1974)	HCC (n=106)	No HCC (n=1868)
Follow-up time, months	29.4 (12.8–47.2)	13.7 (6.3–21.3)	31.1 (13.4–48.0)
Age	55.0 (45.0–62.6)	59.0 (54.0–64.0)	54.5 (44.5–62.4)
Male	1233 (62.5%)	83 (78.3%)	1150 (61.6%)
BMI, kg/m^2‡	26.4 (23.0–30.5)	25.9 (23.4–29.0)	26.4 (22.9–30.7)
Etiology			
ALD	434 (22.0%)	30 (28.3%)	404 (21.6%)
MASLD	412 (20.9%)	9 (8.5%)	403 (21.6%)
HCV	296 (15.0%)	39 (36.8%)	257 (13.8%)
HCV SVR baseline	80 (27.0%)	2 (5.1%)	78 (30.4%)
HCV SVR follow-up	88 (29.7%)	1 (2.6%)	87 (33.9%)
HBV	211 (10.7%)	15 (14.2%)	196 (10.5%)
HBV control baseline	87 (41.2%)	2 (13.3%)	85 (43.4%)
HBV control follow-up	83 (39.3%)	0 (0.0%)	83 (42.3%)
Previous decompensation	464 (23.5%)	88 (83.0%)	376 (20.1%)
Infections	97 (5.7%)	4 (13.8%)	94 (5.6%)
Ascites	245 (13.1%)	25 (23.6%)	220 (12.4%)
Encephalopathy (West Haven)	65 (3.9%)	6 (20.7%)	59 (3.6%)
HRS	50 (2.9%)	4 (13.8%)	46 (2.7%)
Variceal bleeding	109 (6.4%)	1 (3.4%)	108 (6.5%)
SBP	8 (0.8%)	2 (8.0%)	6 (0.6%)
Laboratory tests			
Albumin, g/l	40.0 (34.0–43.0)	37.0 (32.8–42.0)	40.0 (34.0–43.0)
Alkaline phosphatase, U/l	90.0 (67.0–129.0)	117.0 (86.5–159.0)	89.0 (67.0–126.0)
ALT, U/l	45.0 (28.0–78.0)	41.0 (30.0–69.0)	45.3 (28.0–79.0)
AST, U/l	44.0 (30.0–70.0)	55.0 (45.0–79.5)	43.0 (30.0–69.0)
Bilirubin, mg/dl	0.8 (0.5–1.3)	1.2 (0.8–1.9)	0.8 (0.5–1.3)
Creatinine, mg/dl	0.8 (0.7–1.0)	0.8 (0.7–1.1)	0.8 (0.7–1.0)
INR	1.1 (1.0–1.2)	1.2 (1.1–1.4)	1.1 (1.0–1.2)
Platelets, ×10^9/l	182.0 (124.0–242.0)	117.5 (81.0–162.0)	185.0 (130.0–244.0)
WBC, ×10^9/l	6.2 (5.0–7.9)	5.4 (4.8–7.3)	6.2 (5.0–7.9)
CRP, g/dl	2.9 (1.0–7.0)	3.5 (1.6–8.2)	2.9 (1.0–7.0)
Scores			
MELD	7.7 (6.4–10.5)	9.7 (8.2–13.1)	7.5 (6.4–10.2)
Child–Pugh	5.0 (5.0–5.0)	6.0 (5.0–6.0)	5.0 (5.0–5.0)
Stage A	1714 (86.8%)	84 (79.2%)	1630 (87.3%)
Stage B	215 (10.9%)	18 (17.0%)	197 (10.5%)
Stage C	45 (2.3%)	4 (3.8%)	41 (2.2%)
Liver stiffness			
2D-SWE, kPa	11.2 (7.2–23.0)	22.0 (15.7–30.7)	10.7 (7.1–21.6)
TE, kPa	8.2 (5.7–13.8)	22.6 (17.9–24.0)	8.1 (5.7–13.6)
FIB-4	1.9 (1.1–3.9)	5.1 (2.8–7.3)	1.8 (1.0–3.6)
SAGE	8.0 (5.0–11.0)	11.0 (11.0–13.0)	8.0 (5.0–11.0)
APS	79.0 (61.0–89.0)	87.9 (82.0–92.0)	78.0 (60.0–89.0)

* 2D-SWE denotes two-dimensional shear-wave elastography; ALD, alcohol-related liver disease; ALT, alanine transferase; APS, age, platelets, and two-dimensional shear-wave elastography score; AST, aspartate transaminase; BMI, body mass index; CRP, C-reactive protein; dl, deciliter; FIB-4, fibrosis-4; g, gram; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HE, hepatic encephalopathy; HRS, hepatorenal syndrome; INR, international normalized ratio; kPa, kilopascal; l, liter; MASLD, metabolic dysfunction–associated steatotic liver disease; MELD, Model for End-Stage Liver Disease; mg, milligram; SBP, spontaneous bacterial peritonitis; SVR, sustained viral response; TE, transient elastography; WBC, white blood cell. MELD score range: 6-40 (the higher the score, the higher the 3-month mortality rate of the patients with chronic liver disease. FIB-4 score range: >0 (<1.45 indicates absence of cirrhosis; between 1.45–3.25 are deemed inconclusive; >3.25 indicates advanced fibrosis/cirrhosis). SAGE score range: 0–15 (the higher the score, the higher the 12-year HCC risk, In patients with SAGE score of 0–5, 6–10 and 11–15, the 12-year cumulative HCC probability was 0%, 4.0% and 13.8%). APS, Platelets, 2D Shear-Wave Elastography Score range: 1–139 (the higher the score, the higher the 3-year and 5-year HCC risk.

† Continuous variables are shown as median (interquartile range); categorical variables are shown as number (percentage); P values were compared between the HCC group and the no-HCC group using a nonparametric U test.

‡ The body mass index is the weight in kilograms divided by the square of the height in meters.

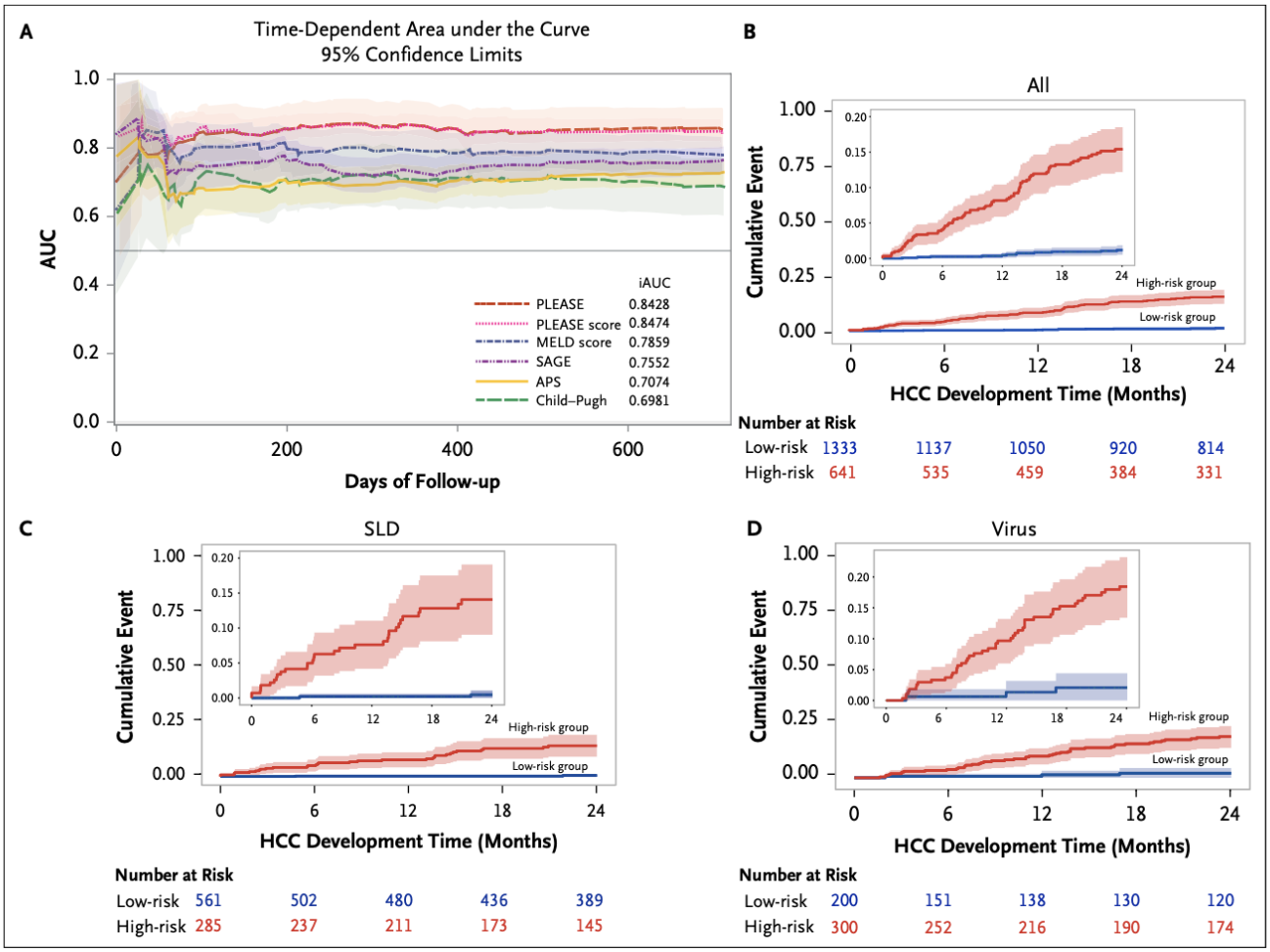
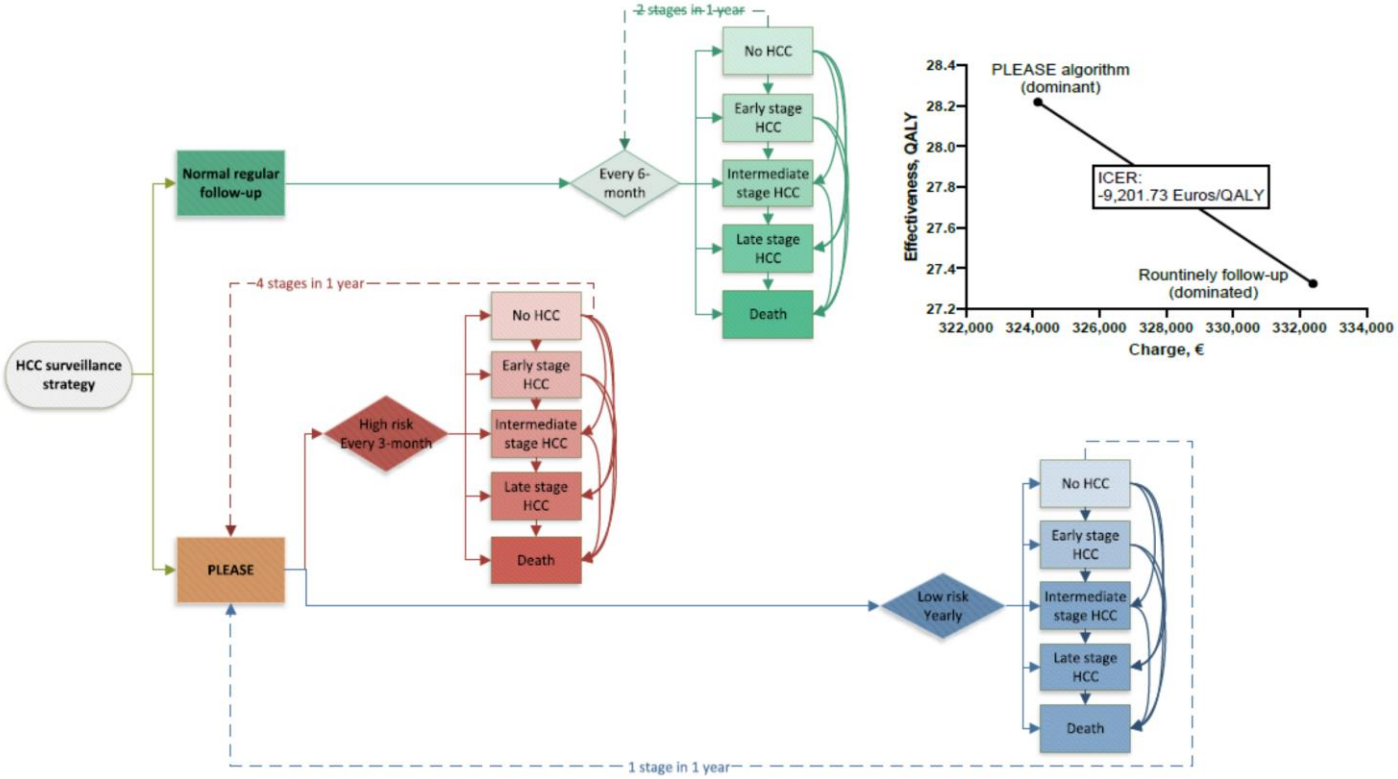


Figure 2. Model Discrimination and Cumulative Hepatocellular Carcinoma Incidence in Different Risk Group.

Panel A: time-dependent area under the curve of the PLEASE algorithm score to predict 2-year de novo HCC development and its comparison with the PLEASE model, MELD score, SAGE score, APS score, and Child–Pugh score. The PLEASE model (red line) indicates the model derived from Cox regression for predicting 2-year HCC. The PLEASE score (pink line) indicates our algorithm score and categorical subscore of 8 (range 0 to 7). Panel B: cumulative event curve of HCC development within 2 years, comparing patients in the low-risk and high-risk groups according to the PLEASE algorithm score in all patients. The inset shows the same data on an enlarged y-axis. Panel C: cumulative event curve of HCC development within 2 years, comparing patients in the low-risk and high-risk groups according to the PLEASE algorithm score in SLD patients. The inset shows the same data on an enlarged y-axis. Panel D: cumulative event curve of HCC development within 2 years, comparing patients in the low-risk and high-risk groups according to the PLEASE algorithm score in viral hepatitis patients. The inset shows the same data on an enlarged y-axis. APS denotes age, platelets, and two-dimensional shear-wave elastography score; AUC, area under the curve; HCC, hepatocellular carcinoma; iAUC, incremental area under the curve; MELD, Model for End-Stage Liver Disease; PLEASE, platelet, elastography, age, sex, and etiologies algorithm; SAGE, stiffness and age; SLD, steatotic liver disease; and SWE, shear-wave elastography.



Πάντζιος Σπυρίδων
Ειδικευόμενος Εσωτερικής Παθολογίας
Πανεπιστημιακή Παθολογική Κλινική – Ηπατογαστρεντερολογική Μονάδα
ΓΟΝΚ «Οι Άγιοι Ανάργυροι»