Σύνοψη AASLD 2023
Καρκίνος ήπατος

Ιωάννης Γουλής

Δ Παθολογική Κλινική ΑΠΘ

Δηλώνω ότι έχω σύγκρουση συμφερόντων (conflict of interest)

- Speaking/Teaching: Gilead, IPSEN, Merck, Roche, ASTRA
- Grant/Research support: ELPEN, Gilead, Novo-Nordisc, Roche

Σύνοψη AASLD 2021
Καρκίνος ήπατος

- 13 προφορικές ανακοινώσεις
- 225 posters
- 2 sessions για ΗΚΚ
- 2 sessions για Χολαγγειο-Ca
- Liver Cancer SIG

Σύνοψη AASLD 2023
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- Επιδημιολογία
- Νέα διαγνωστικά εργαλεία
- Φυσική Ιστορία – Πρόγνωση ΗΚΚ
- Θεραπεία ΗΚΚ
  - Σχήματα ανοσοθεραπείας
  - Ανταπόκριση στη θεραπεία
  - Adjuvant therapy
- Μεταμόσχευση ήπατος και καρκίνος ήπατος
- Διάγνωση χολαγγειο-Ca
- Θεραπεία χολαγγειο-Ca

TEMPORAL TRENDS OF HEPATOCELLULAR CARCINOMA MORTALITY IN THE UNITED STATES FROM 1999 TO 2020

Alexander Kusnik, Sarath Lal Mannumbeth Renjithlal, Keerthi Mannumbeth Renjith, Asim Mushtaq
Department of Internal Medicine, Rochester Regional Health, Rochester, NY, USA

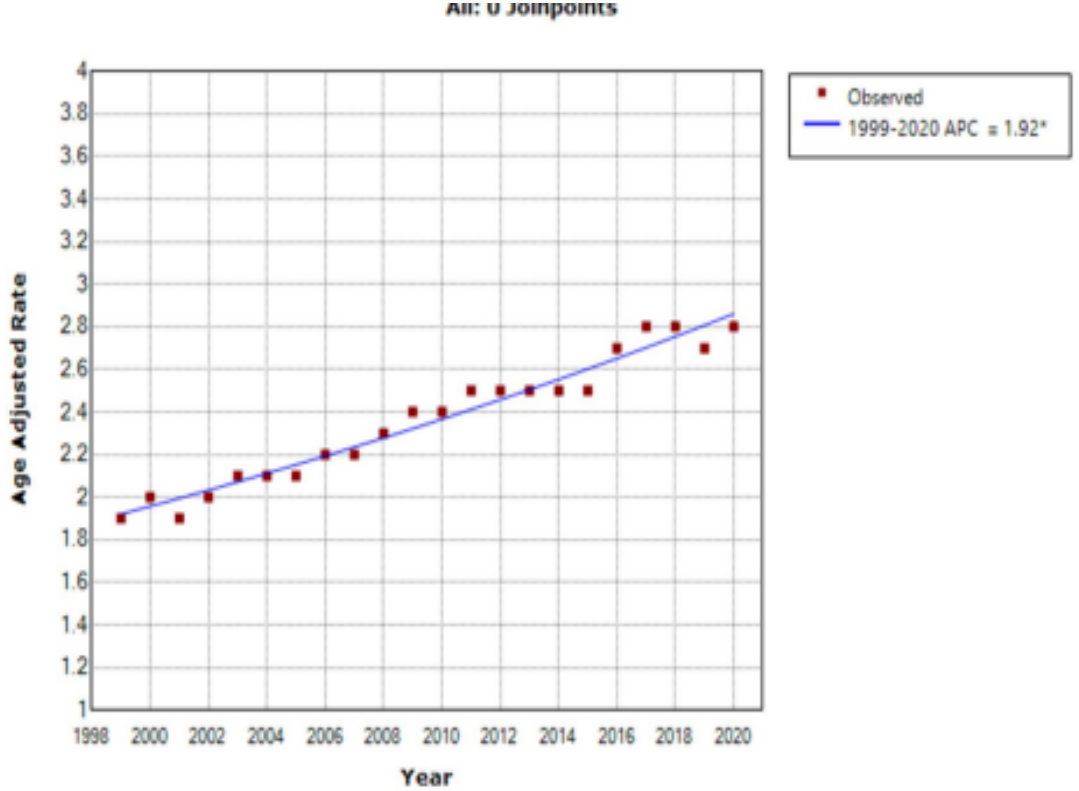

Figure 1 The AAMR for hepatocellular carcinoma per 100,000 population exhibited a significant upward trend over the two-decade study period in the US for the general population

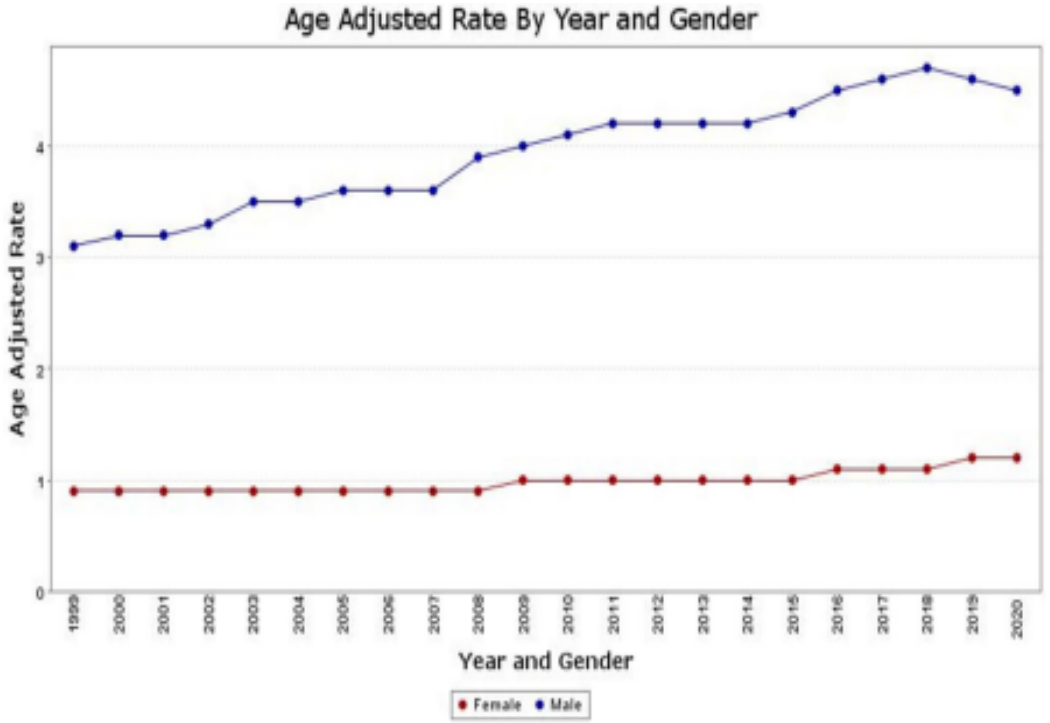

Figure 2 The AAMR for hepatocellular carcinoma per 100,000 population exhibited a significant upward trend over the two-decade study period in the US for male population, relatively stable ranges in female

CLINICAL IMPACT OF CEUS ON INDETERMINATE LIVER NODULES ON MRI: SUB-ANALYSIS FROM A PROSPECTIVE MULTICENTER TRIAL

- **Background:** Contrast-enhanced ultrasound (CEUS) is a promising diagnostic technique for hepatocellular carcinoma (HCC) diagnosis. This study aimed to assess the clinical impact of CEUS specifically in cases where liver lesions were indeterminate on MRI.
- **Methods:** A prospective international multicenter validation study for CEUS LI-RADS (Liver Imaging Reporting And Data System) was conducted between January 2018 and August 2021. A total of 594 patients at risk for HCC were enrolled.
- Tissue histology and CT/MRI imaging follow-up were used as the reference standard.

Kono Y et al

CLINICAL IMPACT OF CEUS ON INDETERMINATE LIVER NODULES ON MRI: SUB-ANALYSIS FROM A PROSPECTIVE MULTICENTER TRIAL

- **Results:** A total of 545 nodules reached a final diagnosis based on the reference standard. Among them, 75 nodules with indeterminate MRI characterization (LR-NC: non categorizable, and LR-3: intermediate probability of HCC) were selected for analysis.
- When LR-NC and LR-3 lesions on MRI (n=75) were combined, CEUS LR-1 (n=2) and LR-2 (n=6), nodules were all benign, CEUS LR-5 (n=13) were all HCC. Two CEUS LR-M from LR-NC and one CEUS LR-TIV from LR-2 were malignant, resulting in a clinical impact in 32% (24/75). CEUS had one false positive LR-M case, which was benign on follow up MRI.

Kono Y et al

CLINICAL IMPACT OF CEUS ON INDETERMINATE LIVER NODULES ON MRI: SUB-ANALYSIS FROM A PROSPECTIVE MULTICENTER TRIAL

- **Conclusion:** CEUS LI-RADS demonstrated high clinical impact in liver nodules with indeterminate MRI characterization accurately, identifying both non-malignant lesions, HCC and other malignancy in 32% of patients. These findings highlight the significant clinical value of CEUS in the characterization and diagnosis of liver lesions, particularly in cases where MRI findings are inconclusive or indeterminate.

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CT-BASED DEEP LEARNING MODEL OF HEPATIC VENOUS PRESSURE GRADIENT FOR PREDICTING THE PROGNOSIS OF HEPATOCELLULAR CARCINOMA WITH TRANSARTERIAL CHEMOEMBOLIZATION (CHANCE-CHESS): A MULTICENTER COHORT STUDY

- **Background:** To evaluate the impact of CT-based deep learning model of hepatic venous pressure gradient (HVPG) on prognosis of hepatocellular carcinoma (HCC) patients treated with transarterial chemoembolization (TACE) and systemic therapy.
- **Methods:** A total of 261 consecutive HCC patients treated with TACE and systemic therapy, and had a contrast-enhanced abdominal CT as part of their pre-surgical work-up, were retrospectively collected between January 2010 and December 2021.
- A CT-based HVPG Score, whose computed formula was: 17.37-4.91*ln(Liver/Spleen volume ratio) +3.8[If presence of peri-hepatic ascites],was used to diagnose portal hypertension (image-based CSPH, iCSPH for short) with a cut-off value 11.606.
- The 3D liver and spleen volume were automate calculated by a deep learning segmentation model

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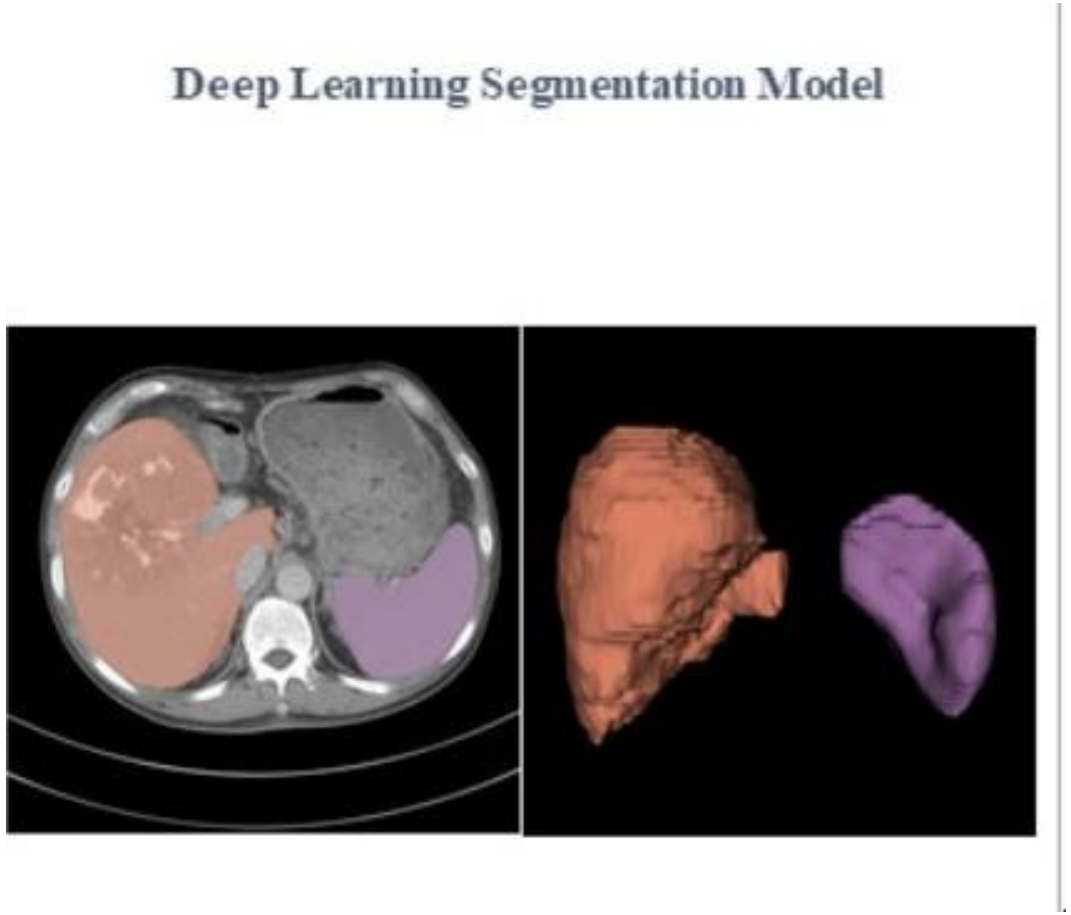
CT-BASED DEEP LEARNING MODEL OF HEPATIC VENOUS PRESSURE GRADIENT FOR PREDICTING THE PROGNOSIS OF HEPATOCELLULAR CARCINOMA WITH TRANSARTERIAL CHEMOEMBOLIZATION (CHANCE-CHESS): A MULTICENTER COHORT STUDY



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CT-BASED DEEP LEARNING MODEL OF HEPATIC VENOUS PRESSURE GRADIENT FOR PREDICTING THE PROGNOSIS OF HEPATOCELLULAR CARCINOMA WITH TRANSARTERIAL CHEMOEMBOLIZATION (CHANCE-CHESS): A MULTICENTER COHORT STUDY

- **Results:** Among 261 patients, 80(30.7%) were diagnosed with iCSPH by CT-based HVPG Score. The median OS in iCSPH group was significantly shorter than non-iCSPH group (16.9 months vs. 20.7 months, P=0.022). Multivariable analysis indicated that the presence of iCSPH was a negative prognostic factor for OS (adjusted hazard ratio [HR], 1.423, P=0.045).

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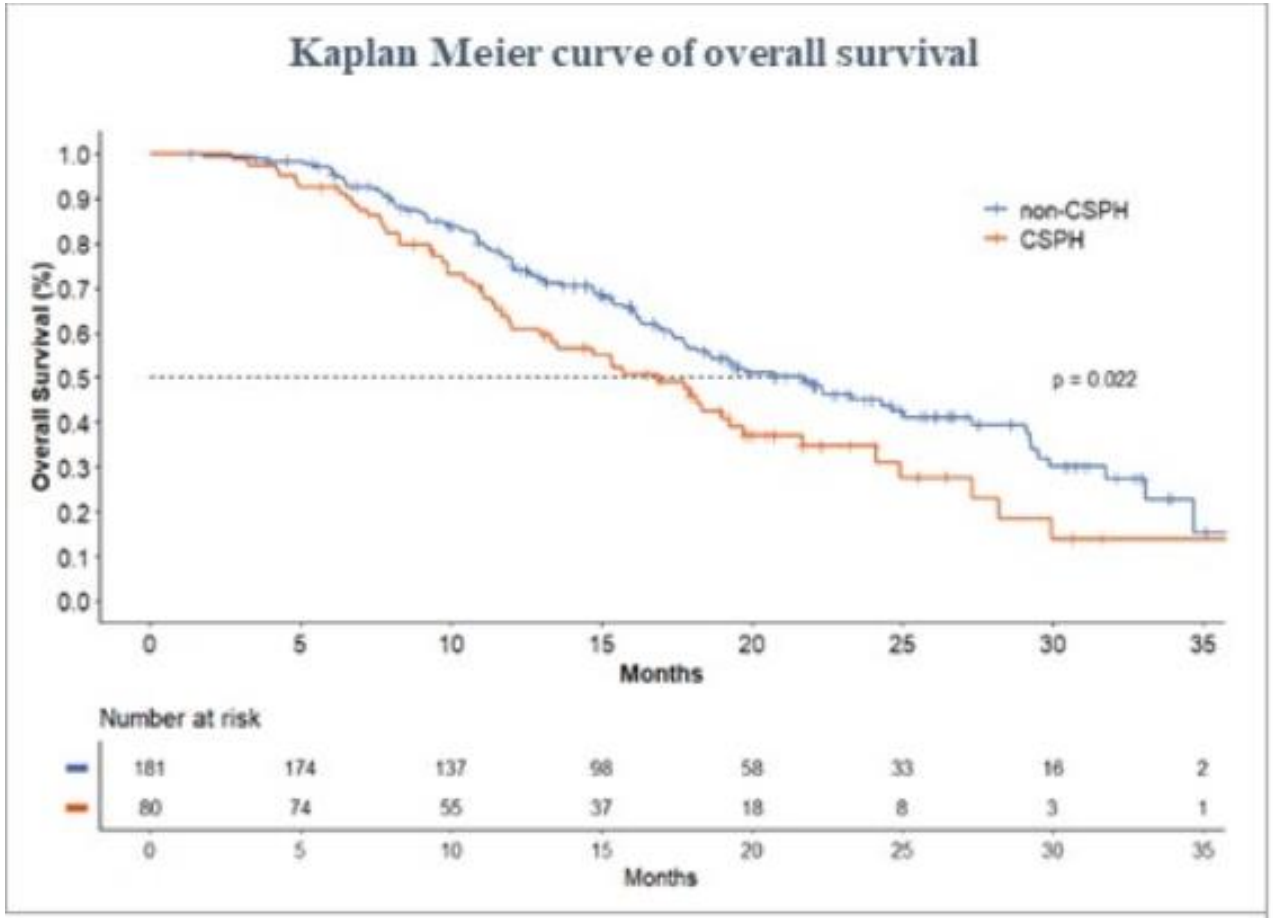
CT-BASED DEEP LEARNING MODEL OF HEPATIC VENOUS PRESSURE GRADIENT FOR PREDICTING THE PROGNOSIS OF HEPATOCELLULAR CARCINOMA WITH TRANSARTERIAL CHEMOEMBOLIZATION (CHANCE-CHESS): A MULTICENTER COHORT STUDY



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CT-BASED DEEP LEARNING MODEL OF HEPATIC VENOUS PRESSURE GRADIENT FOR PREDICTING THE PROGNOSIS OF HEPATOCELLULAR CARCINOMA WITH TRANSARTERIAL CHEMOEMBOLIZATION (CHANCE-CHESS): A MULTICENTER COHORT STUDY

Risk Factors for Overall Survival

	Univariable analysis			Multivariable analysis		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Sex (male vs. female)	0.584	0.369-0.922	0.021	0.643	0.402-1.028	0.065
ECOG PS (1 vs. 0)	1.219	0.866-1.716	0.256			
BCLC Stage (Ref: A)			0.004			0.091
B	1.568	0.774-3.177	0.212	1.334	0.645-2.759	0.438
C	2.475	1.291-4.747	0.006	2.025	0.979-4,190	0.057
Cirrhosis (present vs. absent)	1.251	0.848-1.845	0.259			
HBV (present vs. absent)	0.877	0.610-1.261	0.478			
Child-Pugh class (B vs. A)	1.426	0.952-2.138	0.085			
Six-to-twelve (Ref: < 6)			0.007			0.058
⩾6 & ⩽12	1.616	1.020-2.561	0.041	1.521	0.942-2.457	0.086
> 12	2.164	1.340-3.492	0.002	1.854	1.117-3.078	0.017
Vascular invasion (present vs. absent)	1.516	1.092-2.104	0.013	0.905	0.584-1.402	0.655
Extrahepatic spread (present vs. absent)	1.358	0.975-1.892	0.070			
iCSPH (present vs. absent)	1.491	1.058-2.101	0.023	1.423	1.007-2.010	0.045

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CT-BASED DEEP LEARNING MODEL OF HEPATIC VENOUS PRESSURE GRADIENT FOR PREDICTING THE PROGNOSIS OF HEPATOCELLULAR CARCINOMA WITH TRANSARTERIAL CHEMOEMBOLIZATION (CHANCE-CHESS): A MULTICENTER COHORT STUDY

- **Conclusion:** The segmentation model shows good performance in liver and spleen segmentation in HCC patients, which may help non-invasive HVPG assessment and other CT imaging studies in HCC patients. CT-based HVPG Score was significantly associated with poor outcome and should be taken into consideration when managing HCC patients underwent TACE and systemic therapy.

Wang Y et al

A LIVER STIFFNESS-BASED AETIOLOGY-INDEPENDENT MACHINE LEARNING ALGORITHM TO PREDICT HEPATOCELLULAR CARCINOMA

- **Background:** The existing hepatocellular carcinoma (HCC) risk scores have modest accuracy and most are specific to chronic hepatitis B. In this study, we developed and validated a liver stiffness-based machine learning algorithm (ML) for prediction and risk stratification of HCC in various chronic liver diseases (CLDs).
- **Methods:** MLs were trained for prediction of HCC in 5155 adult patients with various CLDs in Korea and further tested in two prospective cohorts from Hong Kong (HK, N=2732) and Europe (N=2384).

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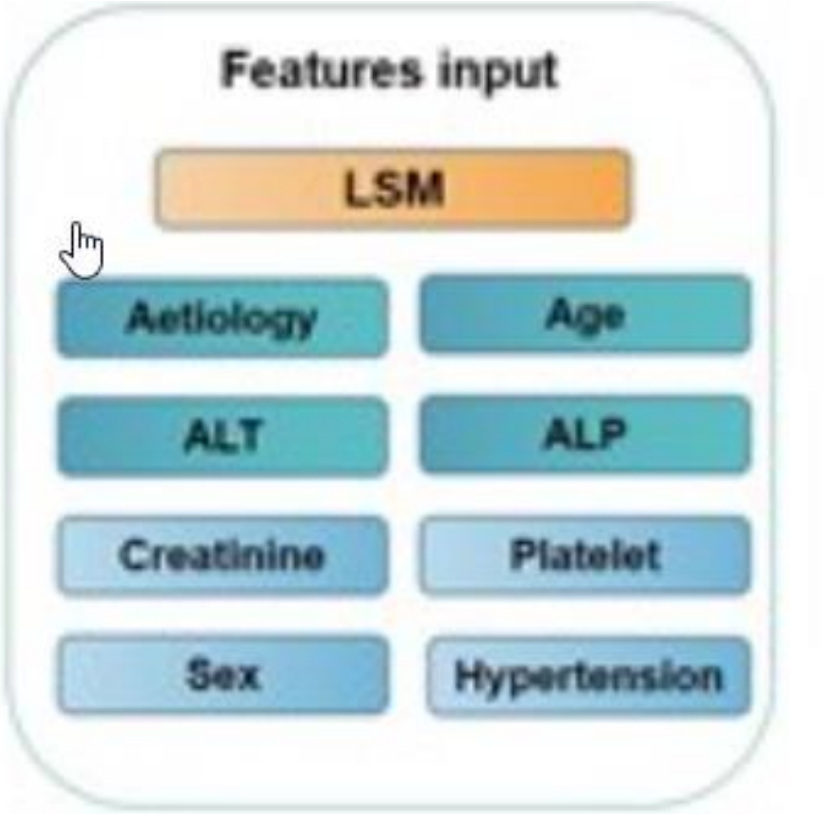
A LIVER STIFFNESS-BASED AETIOLOGY-INDEPENDENT MACHINE LEARNING ALGORITHM TO PREDICT HEPATOCELLULAR CARCINOMA



Cheung-Funk Yip et al

- **Results:** Using a cutoff of 0.045, 82.7% and 89.0% of patients in HK and Europe validation cohorts were classified as low-risk for a possible exemption from HCC surveillance, respectively; the annual HCC incidence for low-risk group was 0.10%-0.19%. The high-risk group had an annual HCC incidence of 1.91% and 2.63% in the HK and Europe validation cohorts, respectively.
- **Conclusion:** The LSM-XGB HCC score is a useful machine learning-based tool for clinicians to stratify HCC risk in patients with CLDs.

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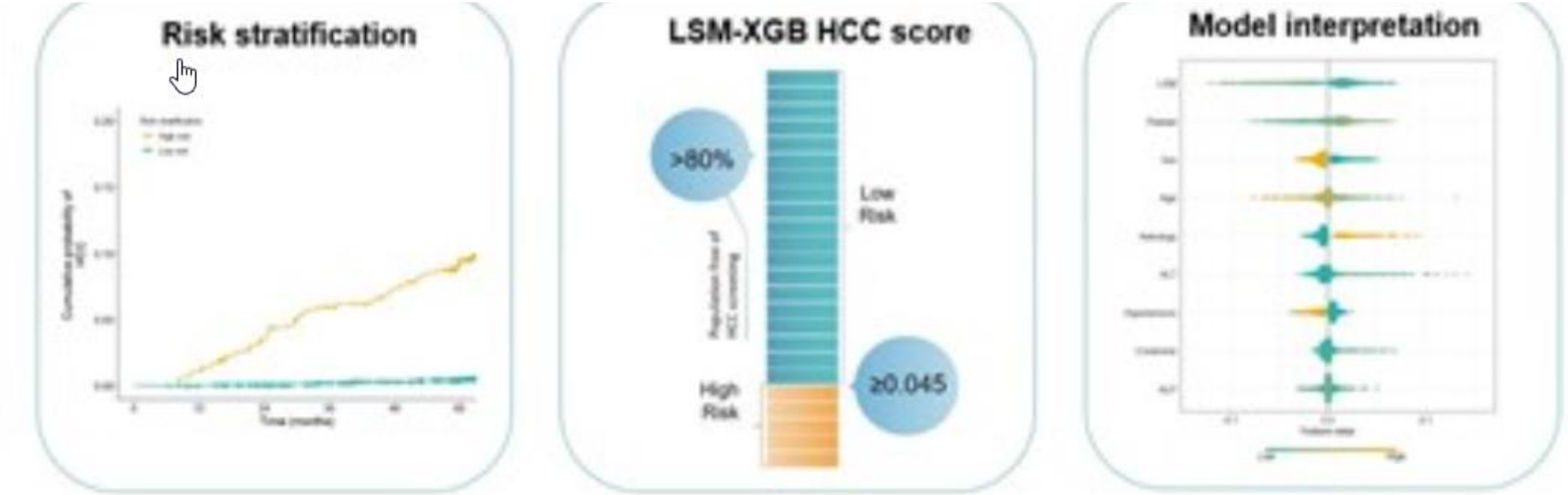
A LIVER STIFFNESS-BASED AETIOLOGY-INDEPENDENT MACHINE LEARNING ALGORITHM TO PREDICT HEPATOCELLULAR CARCINOMA



FOUR-YEAR OVERALL SURVIVAL UPDATE FROM THE PHASE 3 HIMALAYA STUDY OF TREMELIMUMAB PLUS DURVALUMAB IN UNRESECTABLE HEPATOCELLULAR CARCINOMA

- **Background:**In the primary analysis (data cut-off: 27 August 2021) of the phase 3 HIMALAYA study (NCT03298451) in unresectable hepatocellular carcinoma (uHCC), STRIDE (Single Tremelimumab Regular Interval Durvalumab) significantly improved overall survival (OS) and demonstrated a durable long-term survival benefit versus sorafenib; durvalumab monotherapy was noninferior to sorafenib (Abou-Alfa et al. *NEJM Evid* 2022). Here, we report an updated 4-year OS analysis of HIMALAYA.

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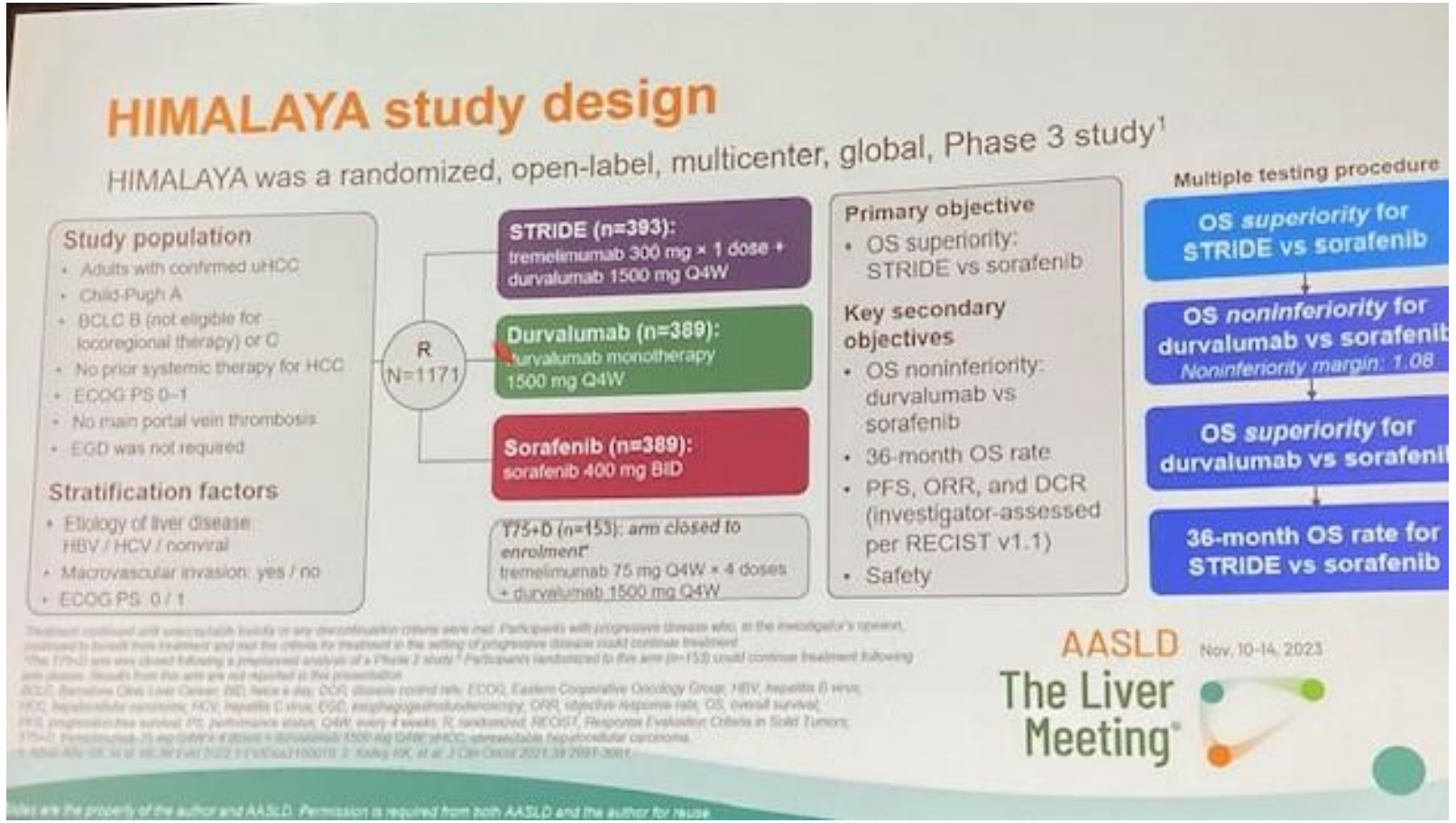

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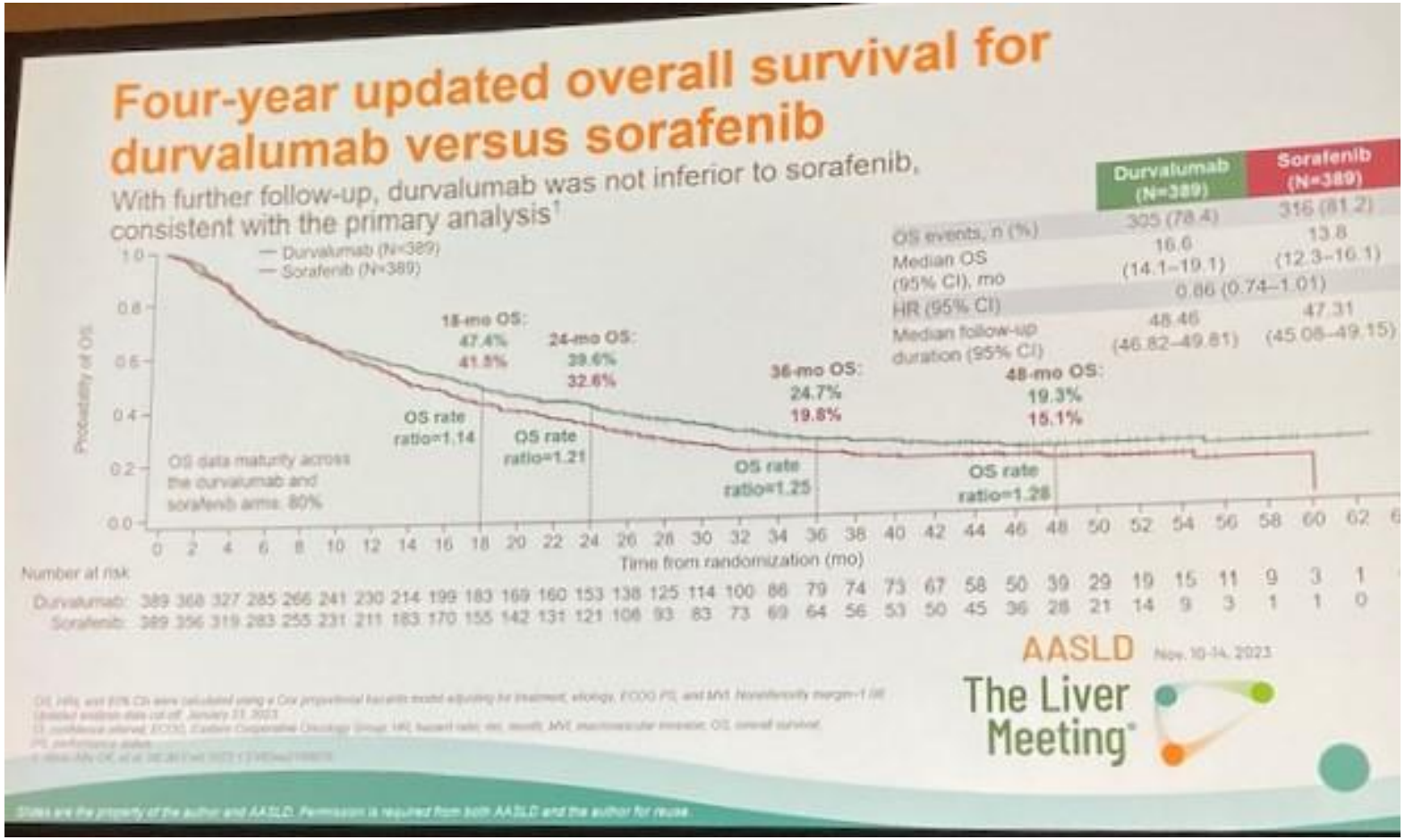

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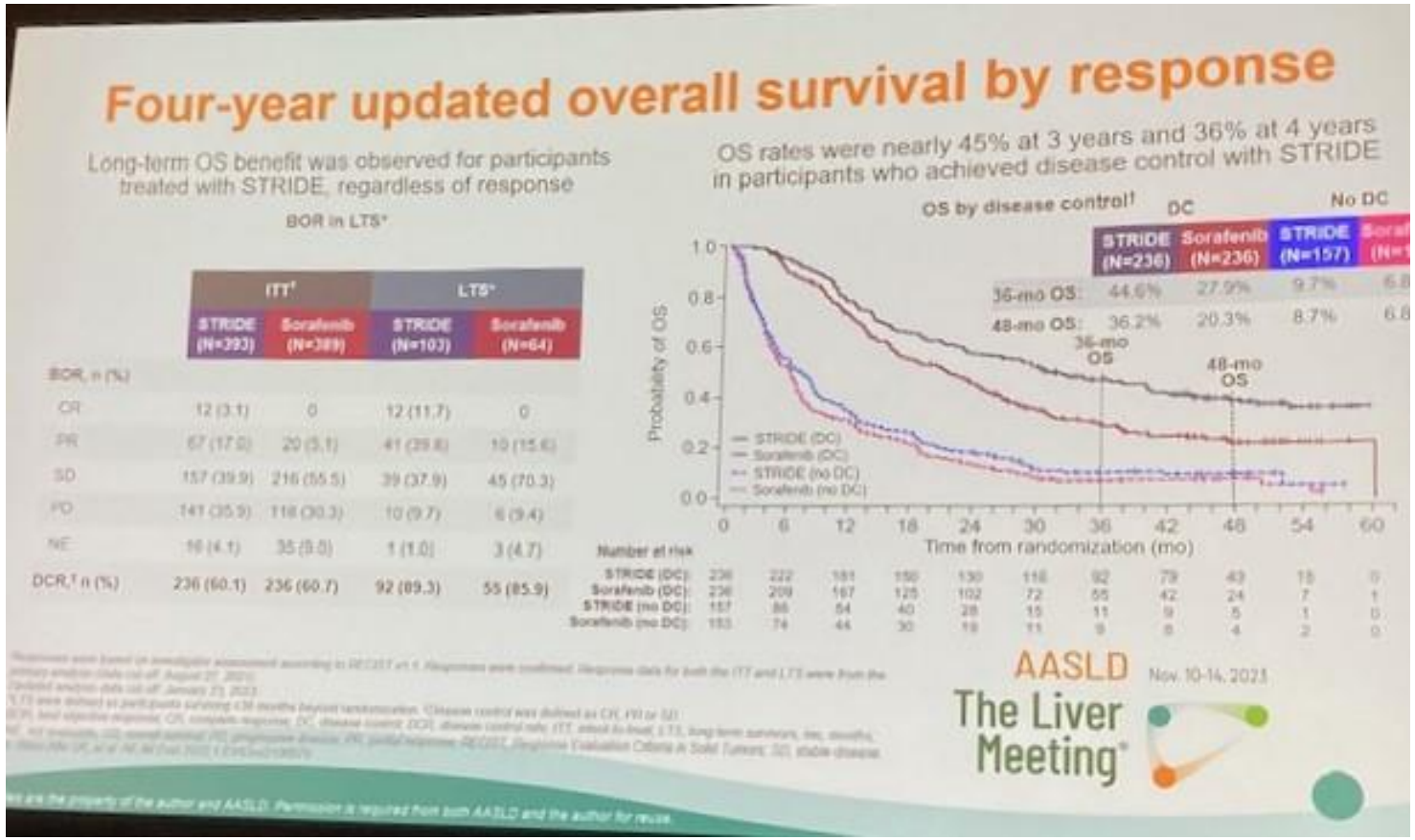

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FOUR-YEAR OVERALL SURVIVAL UPDATE FROM THE PHASE 3 HIMALAYA STUDY OF TREMELIMUMAB PLUS DURVALUMAB IN UNRESECTABLE HEPATOCELLULAR CARCINOMA

- **Results:**
- Follow-up duration was approximately 4 years across treatment arms The 48-month OS rate remained higher for STRIDE (25.2%) versus sorafenib (15.1%).
- No new serious TRAEs occurred after the primary analysis for STRIDE (17.5%). Durvalumab OS noninferiority to sorafenib and safety was consistent with the primary analysis.
- **Conclusion:** These data reinforce the sustained, long-term OS benefit of STRIDE versus sorafenib in a diverse uHCC population, demonstrating unprecedented 3- and 4-year OS rates and longest follow-up to date in phase 3 uHCC studies.

Kelley K et al

ANALYSIS OF IMMUNE-RELATED ADVERSE EVENTS AND TIME-TO-TREATMENT DISCONTINUATION OF ATEZOLIZUMAB AND BEVACIZUMAB IN PATIENTS WITH HEPATOCELLULAR CARCINOMA: A MULTICENTER COHORT STUDY

- **Background:**Pragmatic endpoints, such as time-to-treatment discontinuation (TTD), defined as the duration from starting a medication to the date of treatment discontinuation or death, have been proposed as a potential efficacy endpoint for real-world practice. This study aims to analyze the frequency and severity of immune-related adverse events (irAEs) and TTD in patients with hepatocellular carcinoma (HCC) receiving Atezolizumab and Bevacizumab (A+B) treatment.
- **Methods:**
- This retrospective, multi-center study included consecutive HCC patients who received A+B treatment from September 2020 to December 2022. The primary endpoint of the study was the assessment of TTD and overall survival (OS).

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Adverse events (AEs)
• Immune related adverse events (irAEs); Atezolizumab related
Hepatotoxicities
Colitis
Pancreatitis
Fatigue
Cholangitis
Pneumonitis
Nephritis
Vasculitis
Thyroid (hypothyroidism / thyroiditis)
Skin rash
Infusion-related reaction
Autoimmune hemolytic anemia
• Bevzcizumab related
Variceal bleeding
Proteinuria
Hypertension
Fistula
Thromboembolic events
GI perforation
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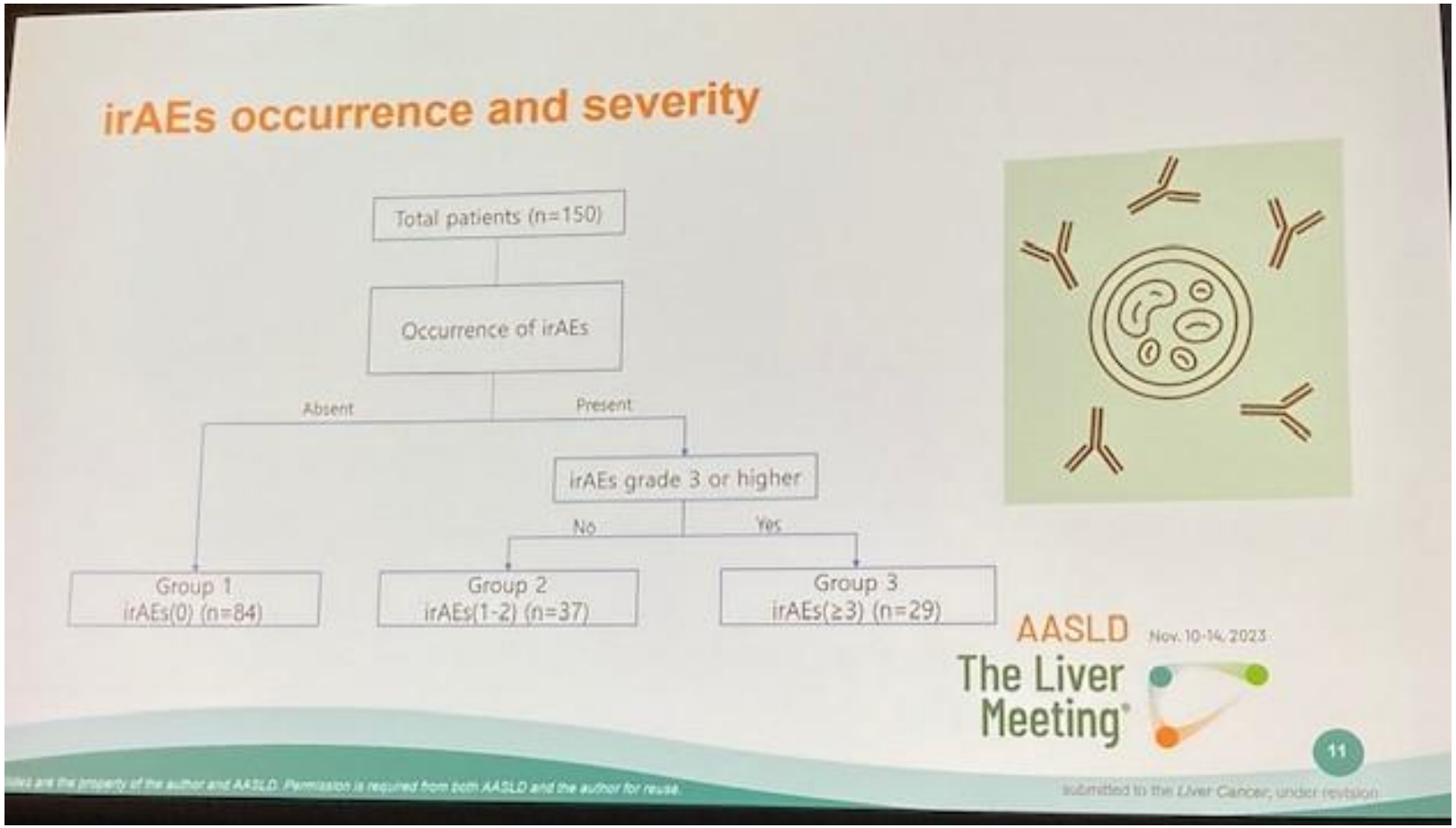
irAEs occurrence and severity
Total patients (n=150)
Occurrence of irAEs
Absent
Present
irAEs grade 3 or higher
No
Yes
Group 1
irAEs(0) (n=84)
Group 2
irAEs(1-2) (n=37)
Group 3
irAEs(≥3) (n=29)
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submitted to the Liver Cancer, under revision

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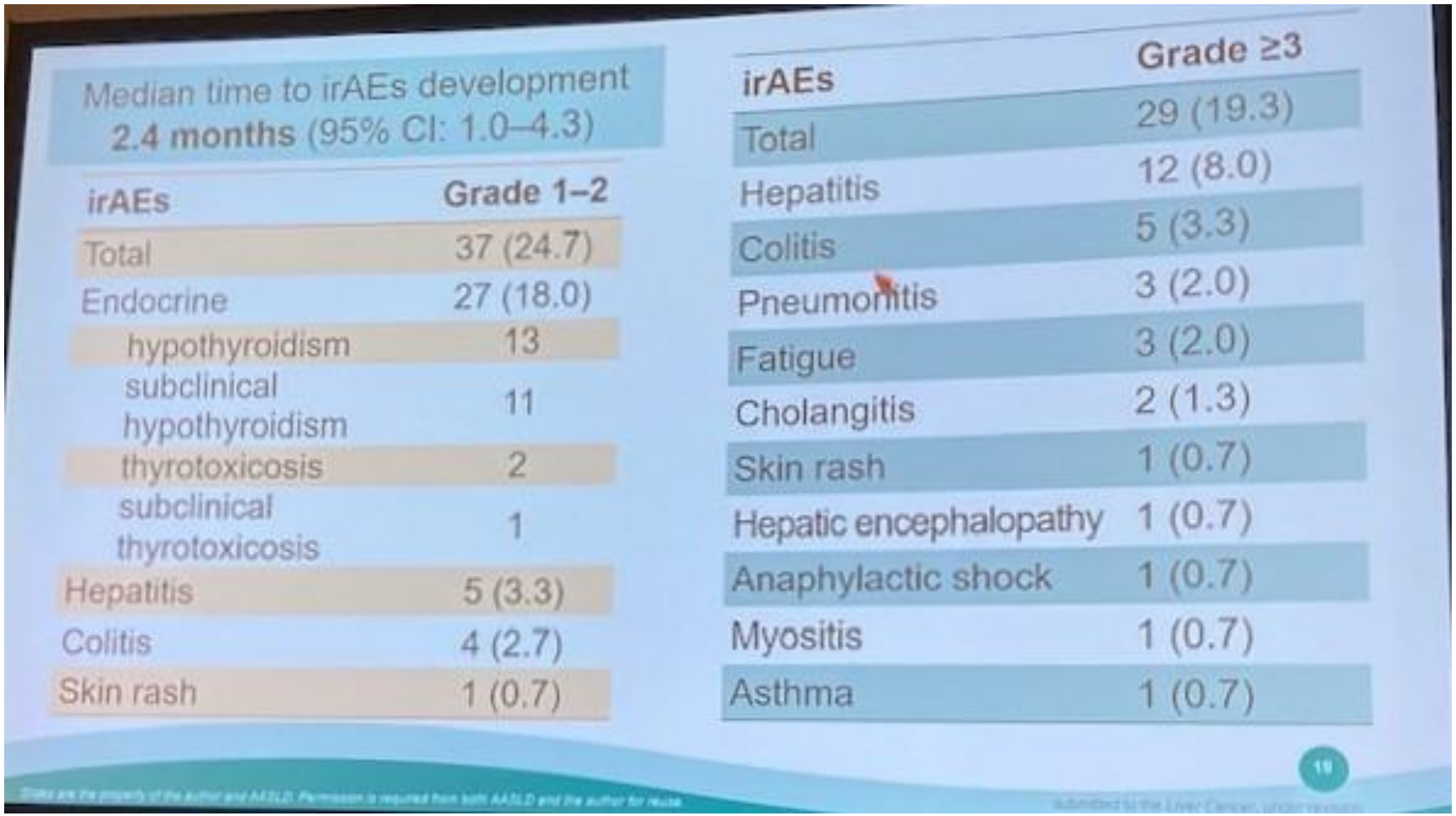

Median time to irAEs development
2.4 months (95% CI: 1.0–4.3)

irAEs	Grade 1–2
Total	37 (24.7)
Endocrine	27 (18.0)
hypothyroidism	13
subclinical hypothyroidism	11
thyrotoxicosis	2
subclinical thyrotoxicosis	1
Hepatitis	5 (3.3)
Colitis	4 (2.7)
Skin rash	1 (0.7)

irAEs	Grade ≥3
Total	29 (19.3)
Hepatitis	12 (8.0)
Colitis	5 (3.3)
Pneumonitis	3 (2.0)
Fatigue	3 (2.0)
Cholangitis	2 (1.3)
Skin rash	1 (0.7)
Hepatic encephalopathy	1 (0.7)
Anaphylactic shock	1 (0.7)
Myositis	1 (0.7)
Asthma	1 (0.7)

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Submitted to the Liver Cancer, under revision

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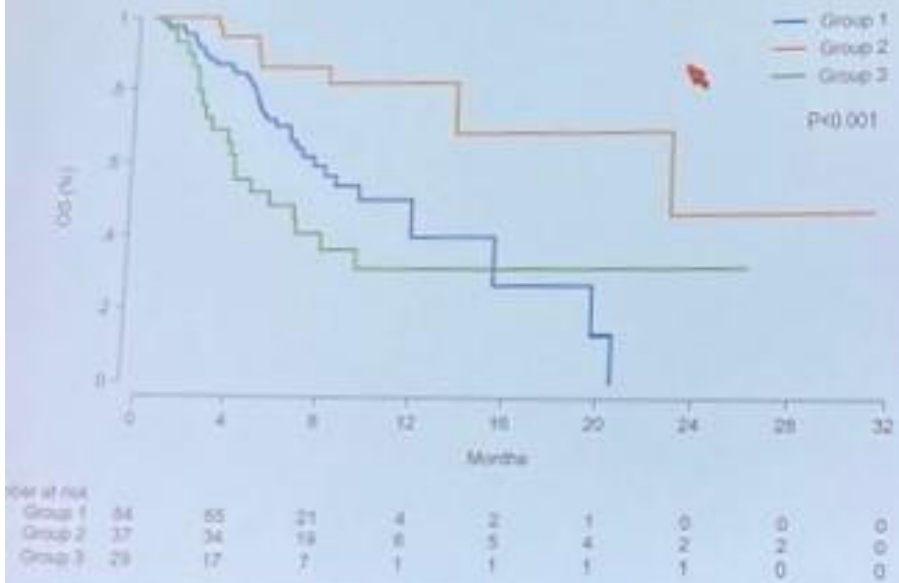
Outcomes; OS



Group 1 No irAEs	9.5 Mo (7.0-19.7)
Group 2 Mild irAEs (1-2)	23.0 Mo (13.6-N/A)
Group 3 Severe irAEs (≥3)	5.6 Mo (2.9-9.5)

	P-value
Group 2 *Vs.* Group 1	0.001
Group 2 *Vs.* Group 3	<0.001
Group 1 *Vs.* Group 3	0.075

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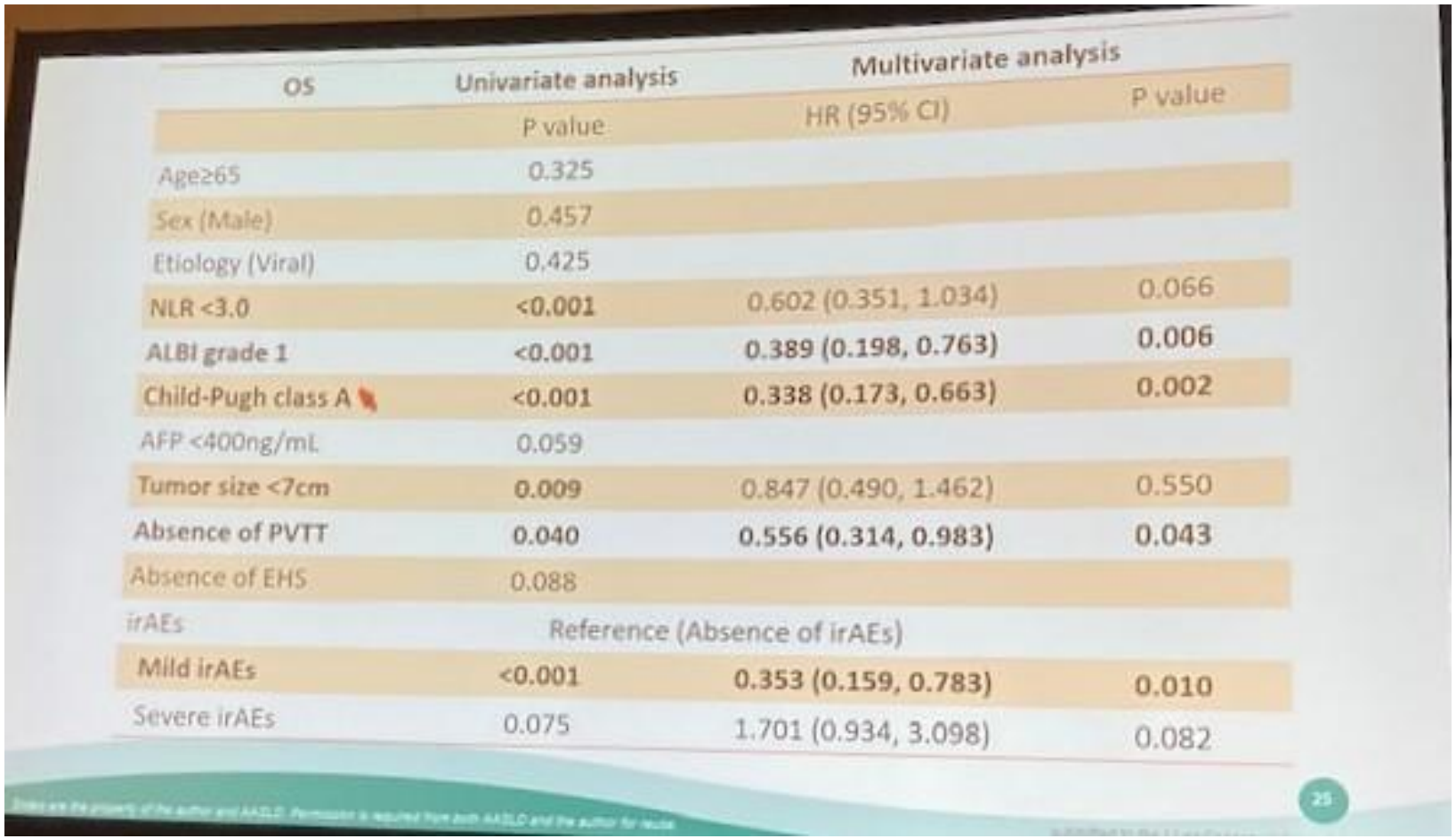

OS	Univariate analysis	Multivariate analysis	
	P value	HR (95% CI)	P value
Age≥65	0.325		
Sex (Male)	0.457		
Etiology (Viral)	0.425		
NLR <3.0	**<0.001**	0.602 (0.351, 1.034)	0.066
ALBI grade 1	**<0.001**	**0.389 (0.198, 0.763)**	**0.006**
Child-Pugh class A	**<0.001**	**0.338 (0.173, 0.663)**	**0.002**
AFP <400ng/mL	0.059		
Tumor size <7cm	**0.009**	0.847 (0.490, 1.462)	0.550
Absence of PVTT	**0.040**	**0.556 (0.314, 0.983)**	**0.043**
Absence of EHS	0.088		
irAEs	Reference (Absence of irAEs)		
Mild irAEs	**<0.001**	**0.353 (0.159, 0.783)**	**0.010**
Severe irAEs	0.075	1.701 (0.934, 3.098)	0.082

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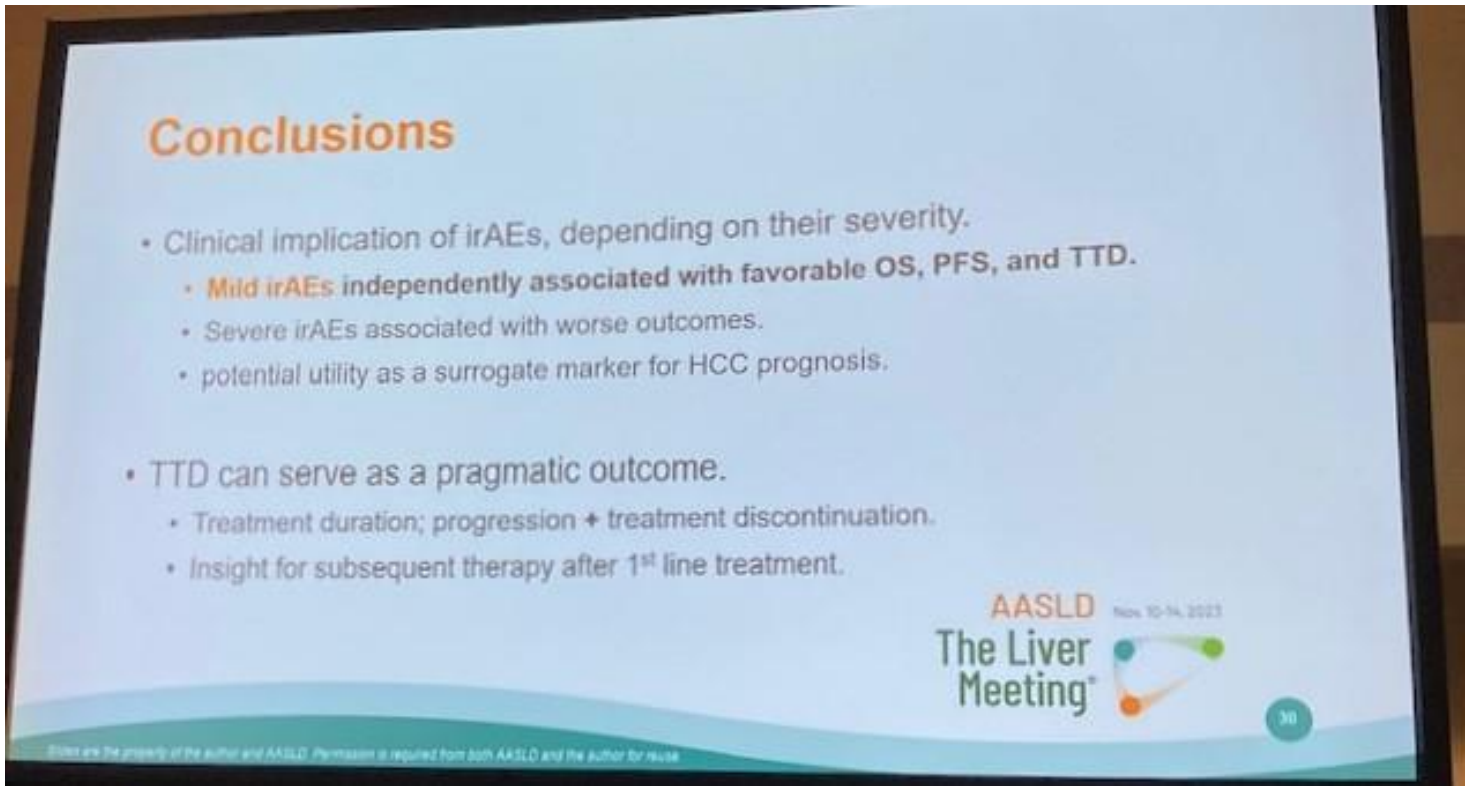
Conclusions
• Clinical implication of irAEs, depending on their severity.
• Mild irAEs independently associated with favorable OS, PFS, and TTD.
• Severe irAEs associated with worse outcomes.
• potential utility as a surrogate marker for HCC prognosis.
• TTD can serve as a pragmatic outcome.
• Treatment duration; progression + treatment discontinuation.
• Insight for subsequent therapy after 1st line treatment.
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Early changes in alpha-fetoprotein are associated with treatment response and overall survival in a real-world cohort of hepatocellular carcinoma patients treated with immune checkpoint inhibitors

Michael Li, MD MPH[1]; R. Kate Kelley, MD[2]; Neil Mehta, MD[1]; Francis Y. Yao, MD[1]; Lawrence Fong, MD[2]; Jennifer C. Lai, MD, MBA[1]

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Results

- 47/173 patients (27%) experienced treatment response
- **The median percent change in AFP was significantly different comparing patients with and without treatment response (-39% vs +11%, p<0.001)**
- As a single predictor of treatment response, percent change in AFP had a c-statistic of 0.80 (Figure 1). **The optimal cutoff for percent change in AFP was -9.7% (sensitivity 75%, specificity 71%).**

Figure 1 – ROC curve, % AFP change as a single predictor of treatment

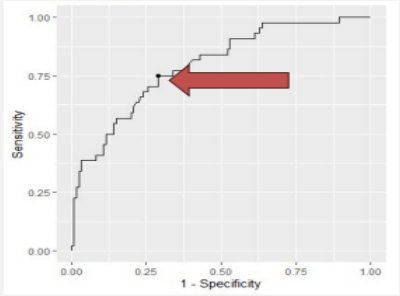
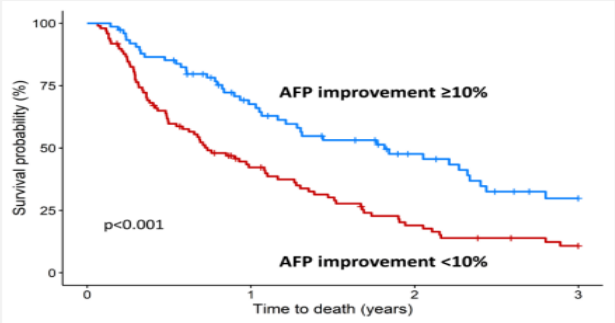
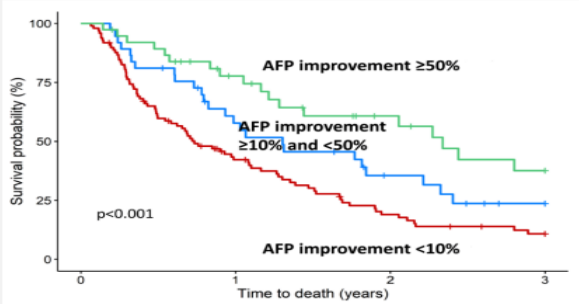


Figure 2 – Time to death stratified by AFP response



- **PRIMARY OUTCOME:** % change in AFP was associated with treatment response (**aOR 1.21 for each 10% reduction in AFP**, 95% CI 1.11-1.33, p<0.001)
  - Similar results were produced when a binary AFP variable using the cutoff of ≥10% reduction was substituted for the continuous AFP variable in the model (**OR 5.33** for patients who had ≥10% early AFP improvement, 95% CI 2.42-11.74, p<0.001)

Figure 3 – Time to death, additional stratification of AFP response



- Improved overall survival was also seen with further stratification of AFP improvement (median 2.34 vs 1.30 vs 0.73 years, log-rank p<0.001; Figure 3)
- Cox regression: ≥10% early AFP improvement was associated with reduced risk of death (HR 0.63, 95% CI 0.45-0.89, p=0.009) after adjusting for ICI regimen, Child-Pugh class, and tumor burden

Discussion

- Early changes in AFP within 2 months of ICI initiation predict treatment response and overall survival in HCC patients
- A cutoff of ≥10% AFP improvement may be clinically useful for early assessment of treatment benefit and in deciding whether to continue ICI

MOLECULAR SIGNATURE OF PERIPHERAL CIRCULATING TUMOR CELLS IN CANCER PROGRESSION OF HEPATOCELLULAR CARCINOMA PATIENTS TREATED BY ATEZOLIZUMAB PLUS BEVACIZUMAB

- **Background:**
- The mechanisms leading to cancer progression of hepatocellular carcinoma (HCC) such as acquired resistance to immunotherapies and metastatic progression are not clear.
- Circulating tumor cells (CTCs) have been defined as cancer cells released into the blood circulation from primary tumor. CTCs have notable advantages in that they are noninvasive and real-time biomarker that provide information about metastatic process.
- CTC analysis has the potential to reveal the mechanism of disease progression and is expected to be applied clinical use such as treatment decision.
- We investigated the changes in CTC counts and gene expression related to cancer progression in patients with unresectable HCC treated by Atezolizumab plus Bevacizumab.

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MOLECULAR SIGNATURE OF PERIPHERAL CIRCULATING TUMOR CELLS IN CANCER PROGRESSION OF HEPATOCELLULAR CARCINOMA PATIENTS TREATED BY ATEZOLIZUMAB PLUS BEVACIZUMAB

- **Results - Conclusion**
- Median CTC counts of PR/SD group decreased at response evaluation, compared with baseline (127 ± 43 vs. 58 ± 6, $p < 0.05$) and is lower compared with PD group at response evaluation (58 ± 6 vs. 153 ± 12, $p < 0.05$).
- GSEA showed that the genes expression of apoptosis signaling pathway (FAS, BCL2) were significantly upregulated in responder group (cluster A).
- TGF-beta signaling pathway-related genes (TGF-β1, SMAD2) were upregulated in non-responder group (cluster B) in clinical course of Atezolizumab plus Bevacizumab ($p < 0.05$).
- CTC in HCC patients treated by immunotherapy may be a notable biomarker that reveal molecular signature of cancer progression.

Murata Y et al

COMPARISON OF RECURRENCE PREDICTION MODELS AND IMBRAVE 050 CRITERIA TO SELECT PATIENTS FOR ADJUVANT IMMUNOTHERAPY AFTER CURATIVE RESECTION OF HEPATOCELLULAR CARCINOMA

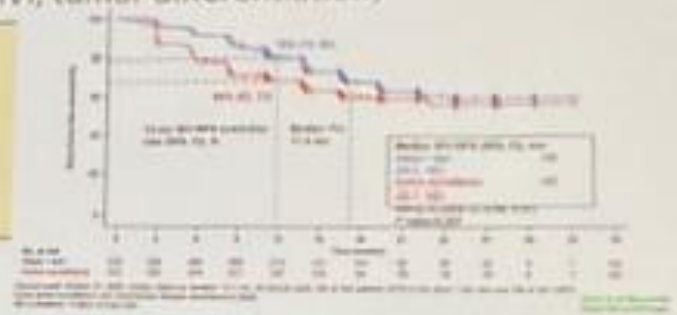
- **Background:**The IMbrave 050 trial recently demonstrated positive results of the adjuvant atezolizumab plus bevacizumab therapy for hepatocellular carcinoma (HCC) patients at high-risk of recurrence after curative treatment. However, the IMbrave 050 criteria to define high-risk of recurrence might be suboptimal. The aim of this study was to compare the performance of current prediction models and IMbrave 050 criteria in predicting recurrence after curative resection for HCC.
- **Methods:**
- Consecutive 1444 HCC patients receiving curative resection were retrospectively enrolled, including 984 (68.1%) patients fulfilling IMbrave 050 high risk criteria. The performance of ERASL-post and an artificial intelligence (AI)-derived clinical-radiomic GARSL postoperative model were compared with IMbrave 050 criteria in predicting recurrence after resection.

I Cheng Lee et al

Background

- HCC recurrence rate after surgical resection remains high (50%–70% at 5 years)[1]
- IMbrave050: positive results of atezo-bev for patients at high risk of recurrence[2]
- However, current criteria to define high risk of recurrence might be suboptimal
  - **IMbrave050 criteria**[2] (4 tumor factors: size, number, MVI, tumor differentiation)

IMbrave050 high risk criteria
1. Up to **3** tumors, largest tumor **>5 cm** regardless of VI or tumor differentiation
2. **≥4** tumors, largest tumor **≤5 cm** regardless of VI or tumor differentiation
3. Up to **3** tumors, largest tumor **≤5 cm with VI** (microVI or minor macroVI Vp1/Vp2), and/or **poor tumor differentiation** (Grade 3 or 4)



  - **ERASL-post model**[3]
    - 4 tumor factors (size, number, MVI, AFP), 2 host factors (gender, ALBI grade)

ERASL-post score = 0.077 × Gender (0: Female, 1: Male) + 0.458 × Albumin-Bilirubin (ALBI) grade (0: Grade 1; 1: Grade 2 or 3) + 0.661 × microvascular invasion (0: no, 1: yes) + 0.082 × ln(Serum AFP in μg/L) + 0.451 × ln(Tumour size in cm) + 0.379 × Tumour number (0: Single; 1: Two or three; 2: Four or more)
Cut-offs to generate the risk groups: ≤2.332 (low), >2.332 to ≤3.445 (intermediate), >3.445 (high)

J Hepatol. 2018;69(6):1284-1293.

1. AASLD Practice Guidance on prevention, diagnosis, and treatment of hepatocellular carcinoma. Hepatology. 2023 May 22. Online ahead of print.
2. IMbrave050 trial: Qin S, et al. Lancet. 2023 Oct 20:S0140-6736(23)01796-8. doi: 10.1016/S0140-6736(23)01796-8.
3. ERASL model: Chan AWH, et al. J Hepatol. 2018;69(6):1284-1293.

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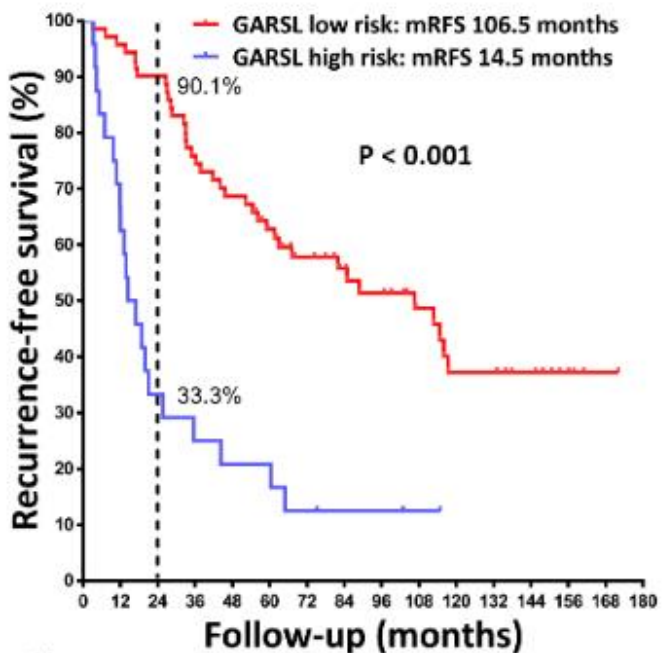
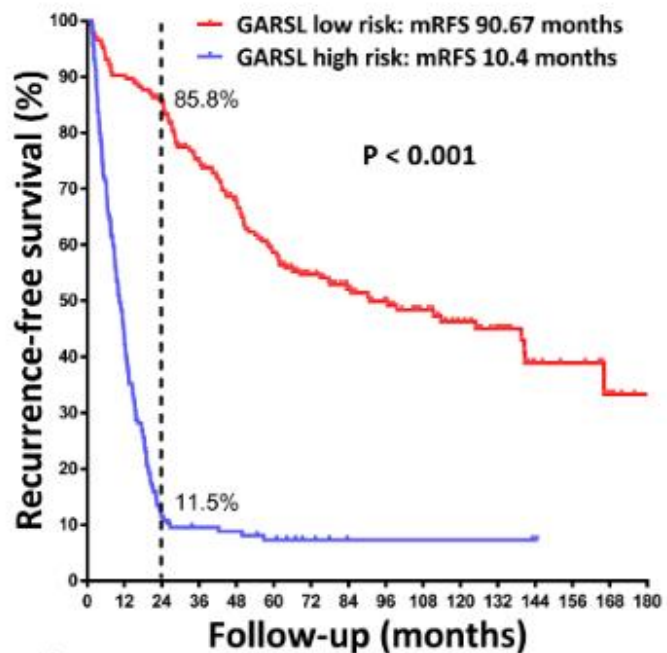
RFS stratified by GARSL-postoperative model

IMbrave 050-low risk



IMbrave 050-high risk

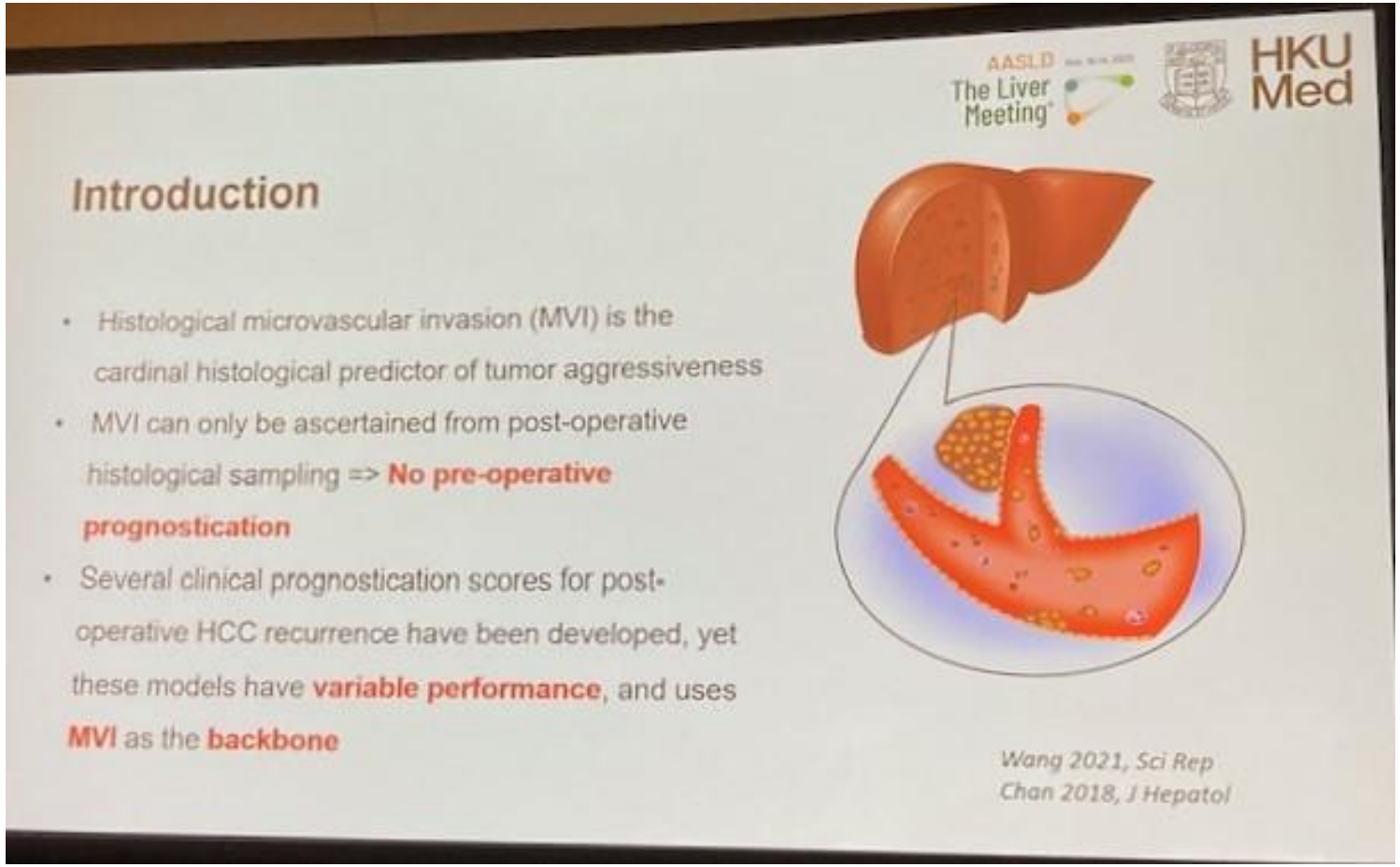


I Cheng Lee et al

- **Conclusion:**
- The high risk patients defined by the IMbrave 050 criteria were heterogeneous and outcomes varied widely. Prediction models using more comprehensive prognostic factors, especially the AI-derived GARSL model, performed better to select high-risk candidates for adjuvant immunotherapy.

I Cheng Lee et al

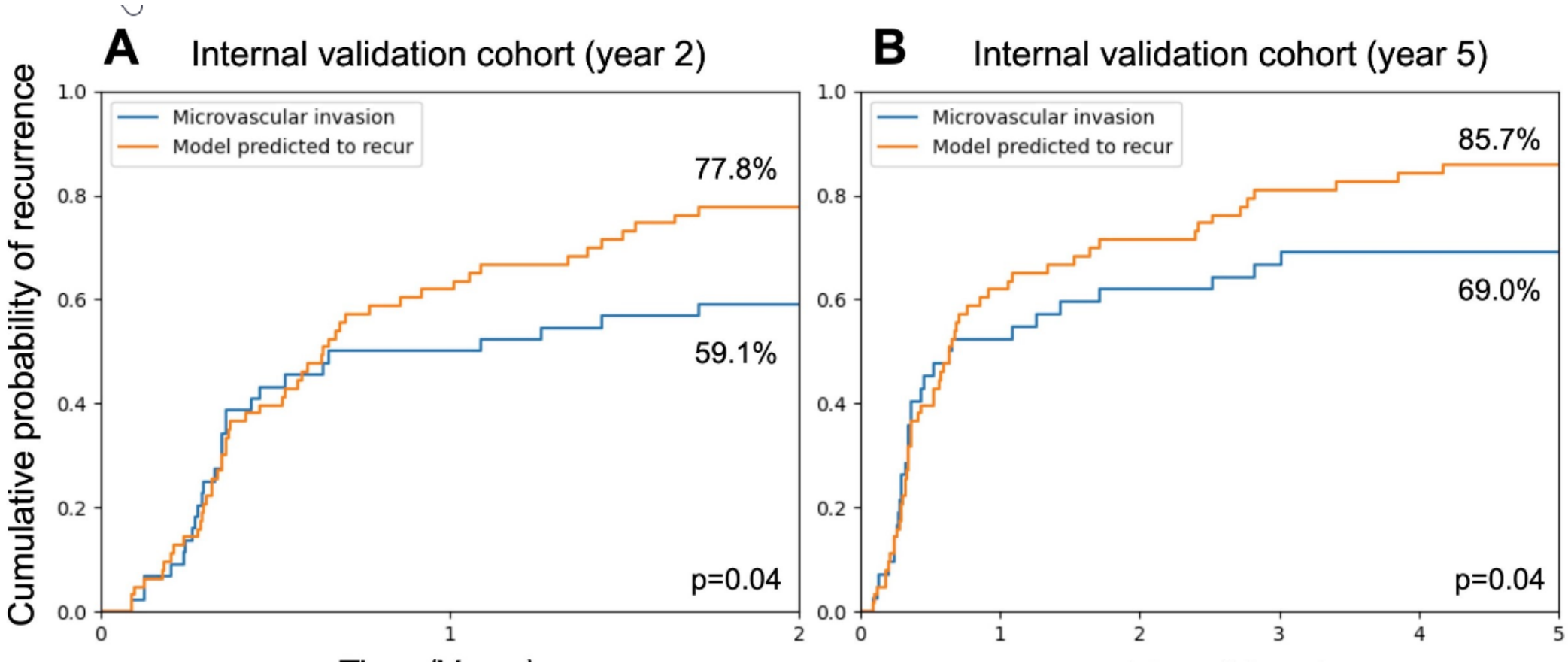
RECURR-NET, A MULTIPHASIC DEEP LEARNING MODEL, IS SUPERIOR TO MICROVASCULAR INVASION IN PREDICTING HEPATOCELLULAR CARCINOMA RECURRENCE AFTER CURATIVE SURGERY: RESULTS FROM INTERNAL VALIDATION AND EXTERNAL TESTING



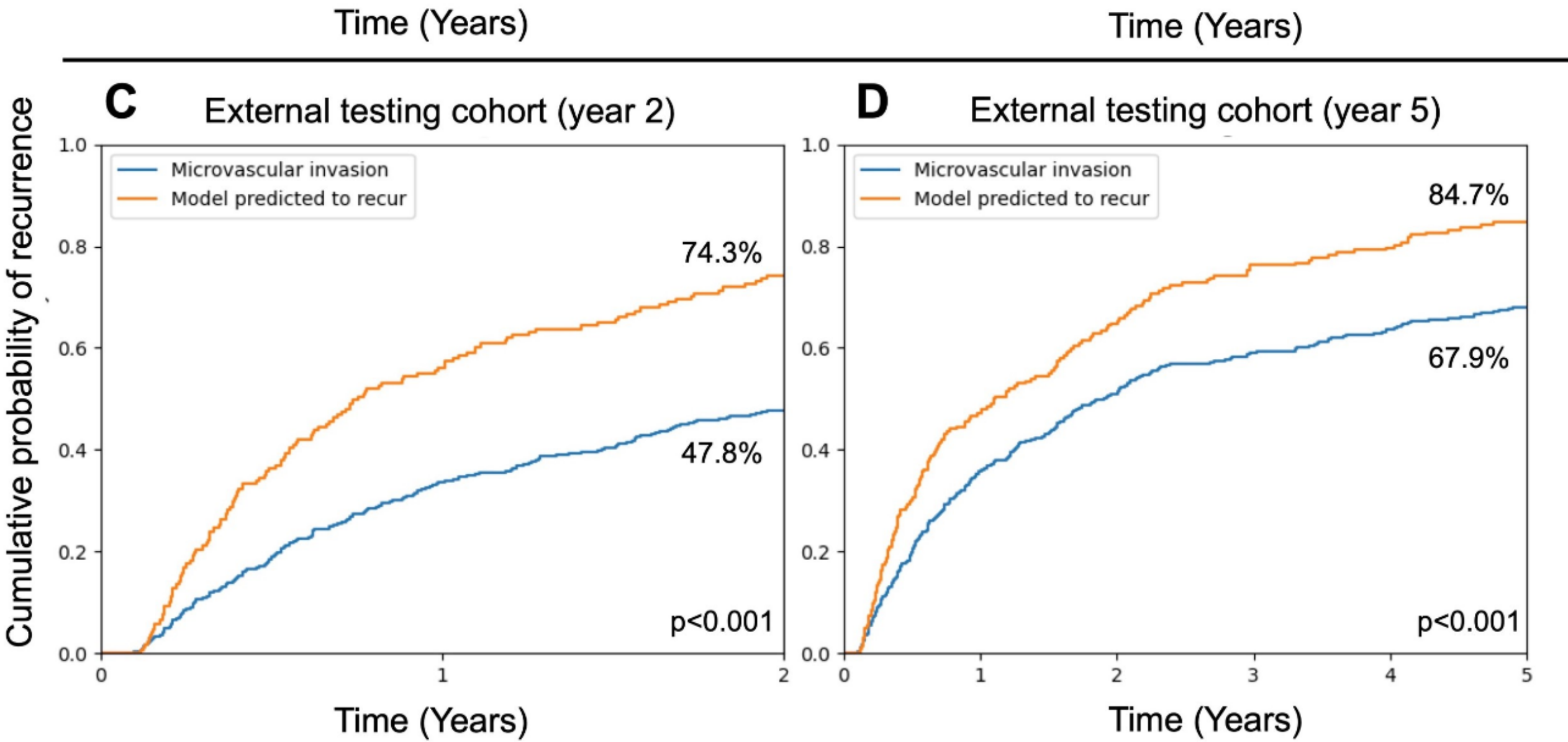
Wan Hin Hui R et al

- We developed an artificial intelligence deep learning-based model using pre-operative computed tomography (CT) for predicting HCC recurrence.
- **Methods:**
- Chinese patients with resected histology-confirmed HCC were recruited from four centers in Hong Kong, and were randomly divided in an 8:2 ratio into training and internal validation groups. We developed Recurr-Net, a multi-phasic residual-network random survival forest deep learning model, incorporating pre-operative triphasic contrast CT images and clinical data (sex, age, comorbidities, blood tests) to predict HCC recurrence. The model was externally tested in an independent cohort from Taiwan.

Wan Hin Hui R et al



Wan Hin Hui R et al



Wan Hin Hui R et al

- **Conclusion:**
- Recurr-NET was superior to MVI in predicting early and late HCC recurrence, and has potential to emerge as a novel tool for pre-operative prognostication of HCC outcomes.

Wan Hin Hui R et al

Validation of the R3-AFP model for risk prediction of HCC recurrence after liver transplantation in the SiLVER clinical trial.

Charlotte Costentin[1*], Federico Piñero[2*], Quirino Lai[3*], Helena Degroote[4], Andreas Schnitzbauer[5], Edward K Geissler[6], Christophe Duvoux[7]

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*Contributed equally.

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Background

- Patients with hepatocellular carcinoma (HCC) are selected for Liver Transplantation (LT) based on pre-LT imaging ± AFP levels [1-3].
- Discrepencies between preLT imaging and explant features are observed in 20-30% of the cases [4].
- Standardized, reproducible, explant-based predictive models of recurrence are needed to reassess the risk of HCC recurrence, guide post-transplant surveillance strategies and potentially immunosuppressive treatment.

[1] Mazzaferro V, et al, N Engl J Med 1996;334:693–9, doi:10.1056/NEJM199603143341104,
[2] Duvoux C, et al, Gastroenterology 2012;143:986–994,e3, doi:10.1053/j.gastro.2012.05.052,
[3] Mazzaferro V, et al, Gastroenterology 2018;154:128–39, doi:10.1053/j.gastro.2017.09.025,
[4] Costentin C, et al, JHEP Rep. 2022 Feb 2;4(5):100445, doi: 10.1016/j.jhepr.2022.100445,
[5] Mehta N, et al, JAMA Oncol. 2017;3(4):493-500,

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Background

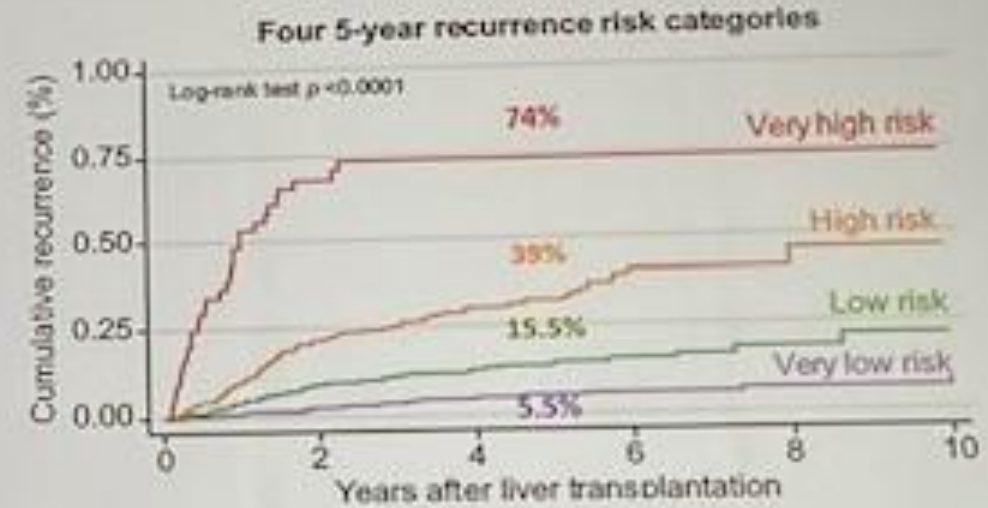
Research article JHEP Reports

R3-AFP score is a new composite tool to refine prediction of hepatocellular carcinoma recurrence after liver transplantation

- Recurrence
- Risk
- Reassessment
- AFP

European derivation cohort (n=1359)
Latin American validation cohort (n=1085)
(clinicaltrials.gov NCT03775863)

R3-AFP variables	Score
Number of nodules	
≥4 nodules	1
Size largest nodule	
≤3 cm	0
3-6 cm	1
>6 cm	5
Vascular invasion	
Yes	2
Nuclear grade >II	
Yes	1
Last pre-LT AFP value (ng/ml)	
<100	0
100-1,000	1
>1,000	2
Recurrence risk categories	
Very low = 0 points	
Low = 1 to 2 points	
High = 3 to 6 points	
Very high >6 points	



Wolber's c-index of 0.78 (95%CI=0,73-0,83)

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Costentin C*, Piñero F* et al, JHEP Reports 2022

Objectives

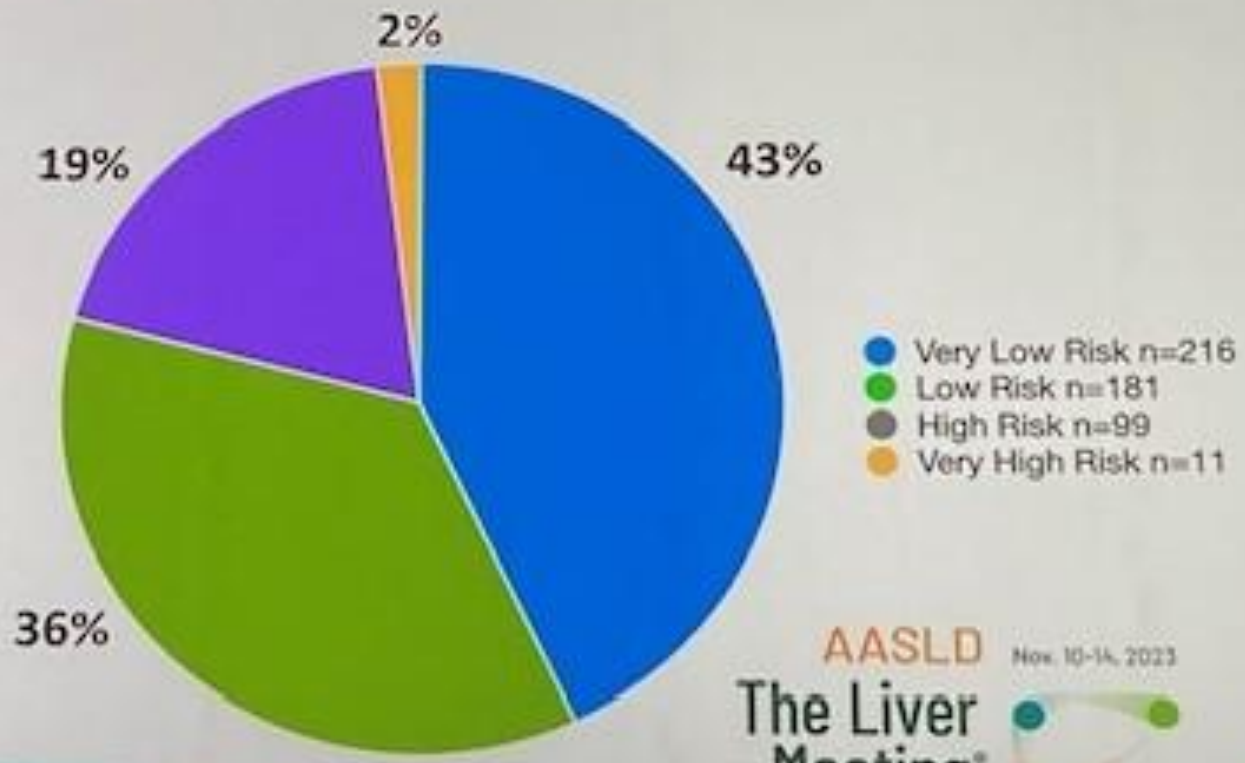
- Validate the R3-AFP model in the ITT population from the prospective *SilVER trial*

Results

R3-AFP variables	Score
<Number of nodules	
≥4 nodules	1
Size largest nodule	
≤3 cm	0
3-6 cm	1
>6 cm	5
Vascular invasion	
Yes	2
Nuclear grade >II	
Yes	1
Last pre-LT AFP value (ng/ml)	
<100	0
100-1,000	1
>1,000	2
Recurrence risk categories	
Very low = 0 points	
Low = 1 to 2 points	
High = 3 to 6 points	
Very high >6 points	

Silver study ITT population

Stratification according to the R3-AFP risk groups



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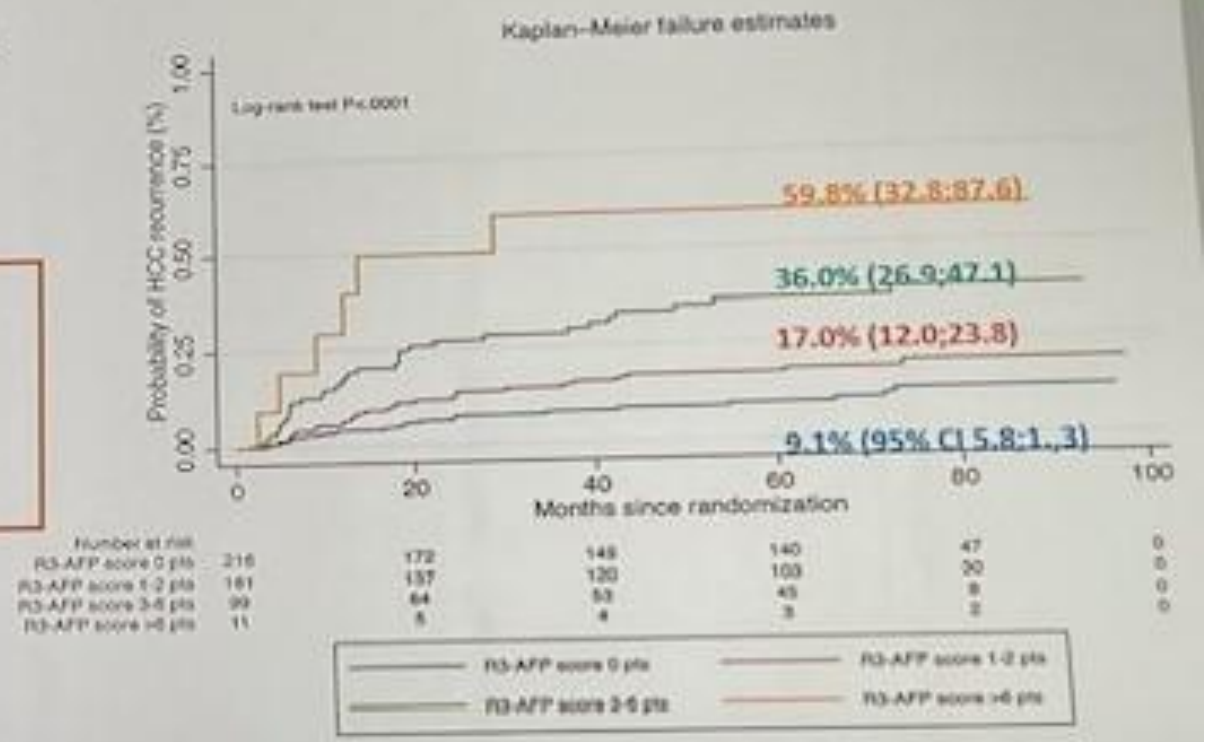
Results

R3-AFP correctly stratified HCC recurrence risk in 4 groups in the ITT population

Overall median follow-up 64 months.

5-year recurrence rate
19% (95% CI 15.3-22.6; n=88 recurrences).



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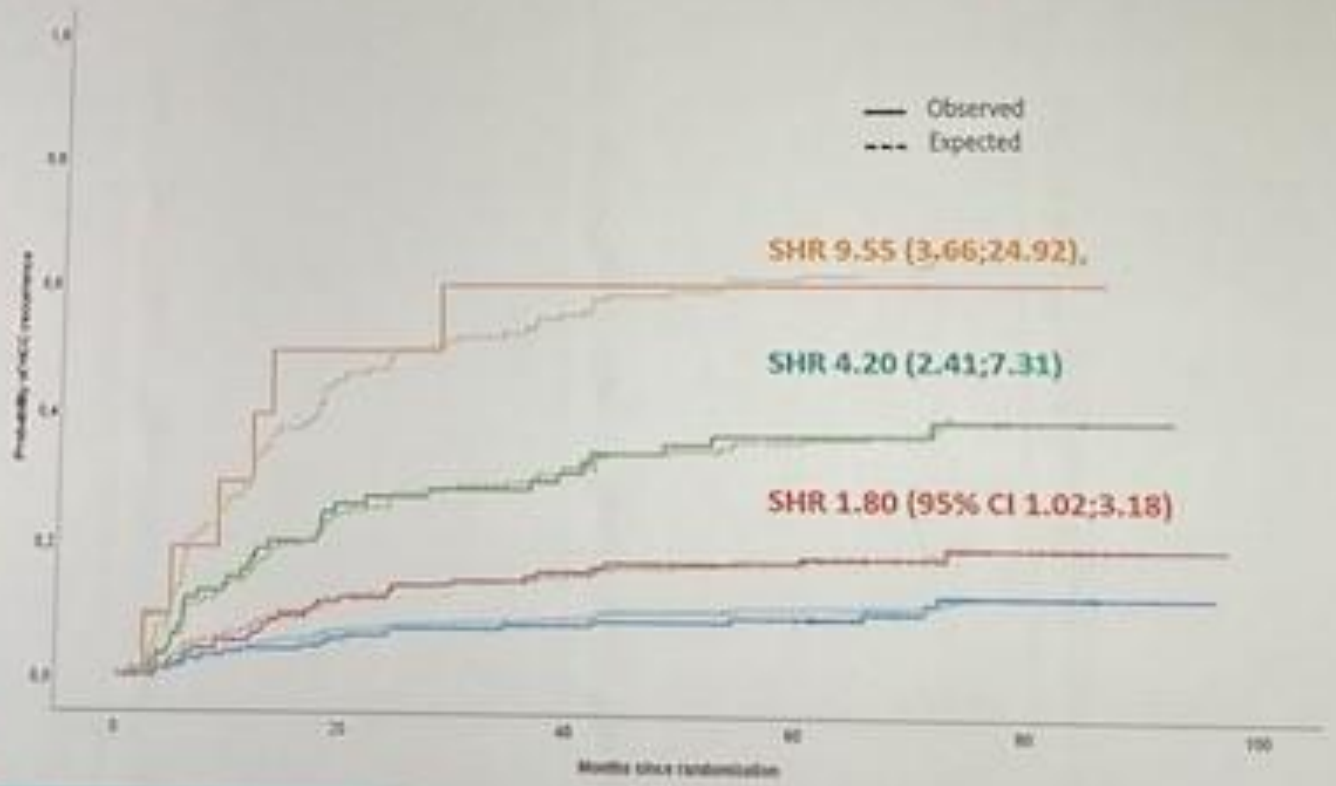
Results

R3-AFP discrimination
c-statistics **0.75 (95% CI 0.69-0.81)**

Calibration between expected and observed events was adequate.



Conclusion

R3-AFP

- has been validated in the ITT population of the prospective SiLVER trial, showing good performance
- can be proposed to reassess the risk of recurrence after LT
- is a robust tool to test surveillance and immunosuppressive strategies post LT tailored to the individual risk of HCC recurrence

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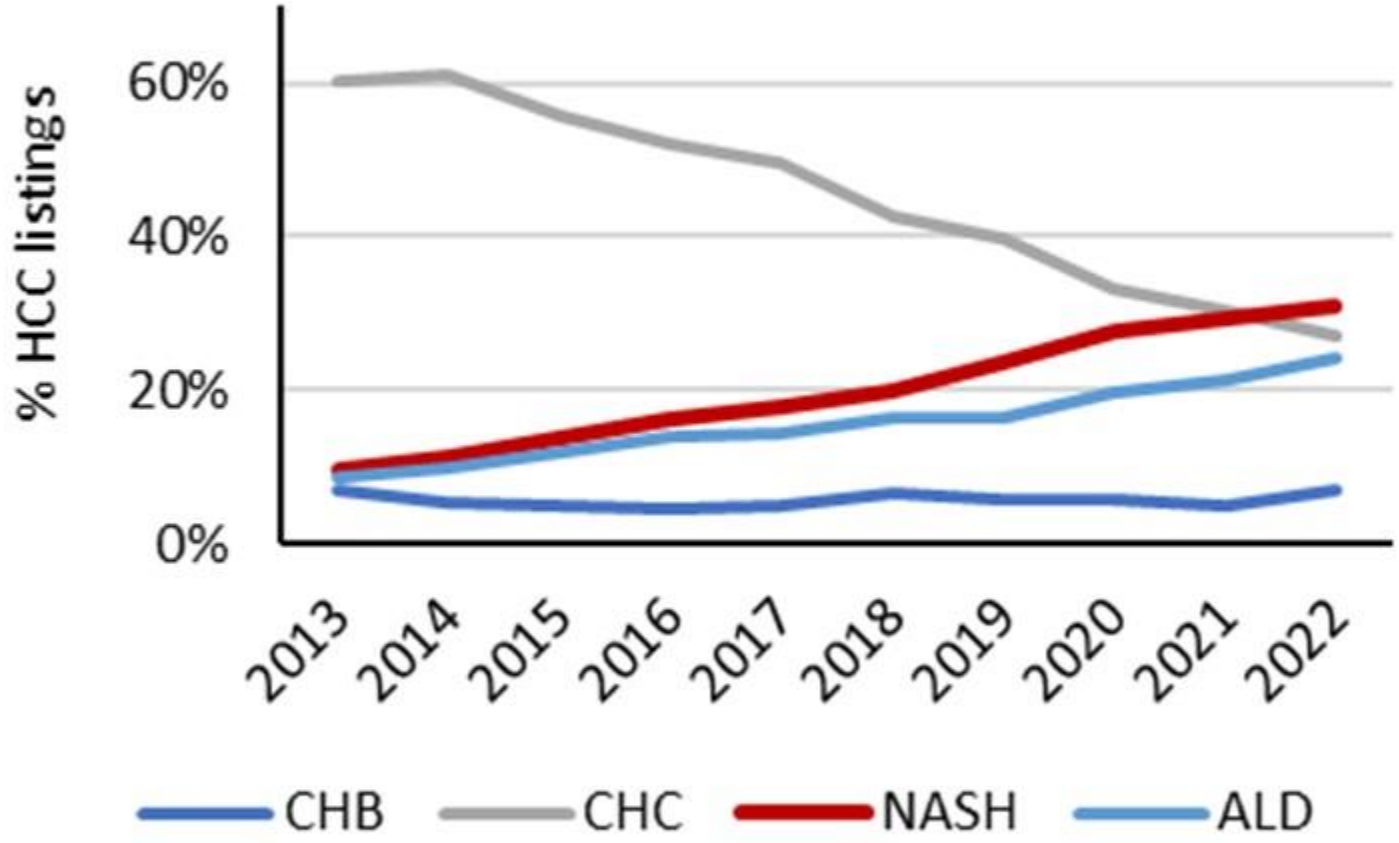
NON-ALCOHOLIC STEATOHEPATITIS (NASH) HAS BECOME THE MOST COMMON INDICATION FOR LIVER TRANSPLANTATION AMONG CANDIDATES WITH HEPATOCELLULAR CARCINOMA IN THE UNITED STATES

- **Methods:**
- The Scientific Registry of Transplant Recipients (SRTR) was used to select adult (>18 years at listing) LT candidates included between 2013-2022.
- **Results:**
- In candidates without HCC, the most common CLD etiology was alcoholic liver disease (ALD) which increased from 23% (2013) to 48% (2022); the most rapid increase happened between 2019-2022 (from 38% to 48%).
- The second most common indication for non-HCC LT was NASH, the proportion of which increased from 19% (2013) to 27% (2022).
- In contrast, rates of chronic hepatitis C (CHC) decreased from 28% (2013) to 4% (2022) and chronic hepatitis B (CHB) declined from 1.8% (2013) to 1.1% (2022) (all trend $p<0.01$).
- Cumulatively, 21% (n=24,657) of candidates listed for LT had HCC.
- However, the proportion of HCC decreased from 24-25% (2013-2016) to 17% (2021-2022).
- Among candidates with HCC, the proportion of CHC decreased from 60% (2013) to 27% (2022) while NASH increased from 10% to 31% and ALD from 9% to 24%, respectively (all trend $p<0.0001$) (**Figure**).
- Among candidates with HCC, the rapid increase in the proportion of NASH continued during the most recent study years: 20% (2018) to 28% (2020) to 31% (2022),. The average magnitude of increase in the proportion of NASH in candidates with HCC in 2018-2022 was +2.8 percentage points per year ($p<0.0001$).

ZM Younossi et al

NON-ALCOHOLIC STEATOHEPATITIS (NASH) HAS BECOME THE MOST COMMON INDICATION FOR LIVER TRANSPLANTATION AMONG CANDIDATES WITH HEPATOCELLULAR CARCINOMA IN THE UNITED STATES



Characterizing the identifying modality of ineligible patients who presented for liver transplantation evaluation for Colorectal Liver Metastases

Eric Takoushian[1], Ellie Brandon[2], Mateo Noriega[2], Pashtoon Kasi[2], Manish Shah[2], Juan P Rocca[2] & Benjamin Samstein[2]
[1]Weill Cornell Medical College, New York, NY [2]Liver Transplantation and Hepatobiliary Surgery, New York Presbyterian Weill Cornell, New York, NY

BACKGROUND

- Liver transplantation is a novel therapy for patients with unresectable colorectal liver metastases (CRLM)
- 5-year survival using liver transplantation appears to be significantly better than systemic chemotherapy in selected patients
- Despite strict criteria for transplantation, there is little guidance on the required workup prior to full transplant evaluation
  - Most referred patients do not proceed to transplantation

Aims

- To identify the necessary screening tests for patients with CRLM referred for liver transplant evaluation
- To describe the reasons many do not progress to transplantation

METHODS

- Prospective cohort of patients with unresectable CRLM referred to NYP-Weill Cornell for liver transplant evaluation since 2018
- Demographic, clinical, and tumor-specific data were collected throughout evaluation
- Key inclusion criteria for CRLM transplant:
  - No evidence of extrahepatic metastases
  - Age 18-65
  - Stability or regression of liver metastases for 6 months

RESULTS

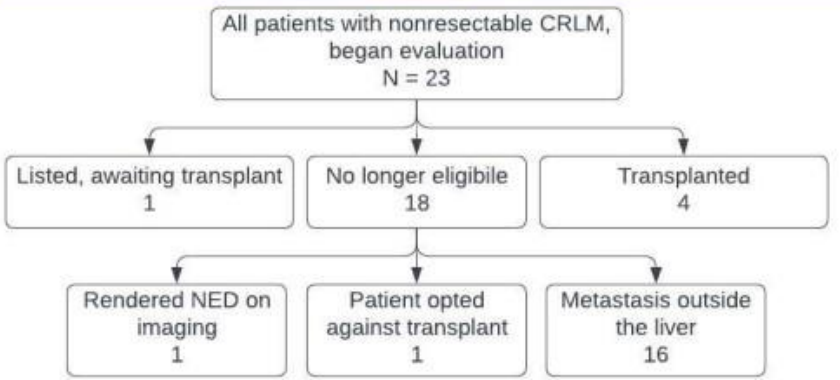
Table 1: Demographics for all patients presenting for transplantation evaluation for CRLM (n=23)

Age at Diagnosis, median (range)	53.8 (29-63)
Sex, n (%)	
Male	21 (91)
Primary Tumor Location, n (%)	
Sigmoid	16 (70)
Primary Tumor intact at referral, n (%)	12 (52)
Prior Resection, Ablation, or HAI pump, n (%)	13 (57)
Number of liver metastases, median (range)	10 (3-20+)
Diameter largest Metastasis, n (%)	
>5.5 cm	10 (43)
CEA at referral, n (%)	
>80	7 (30)
Chemo response, n (%)	
Progression	5 (22)
Oslo Criteria Score, n (%)	
0	4 (17)
1	11 (46)
2	7 (29)
3	1 (4)
Pathology, n (%)	
KRAS mutant	5 (22)

Table 2: Modality to identify ineligibility in patients no longer eligible for transplantation (n=18)

Scan to identify ineligibility, n (%)	
CT chest*	11 (61)

Figure 1: Progression to transplantation and reasons for ending evaluation for all patients presenting for transplantation evaluation for CRLM.



- Overall survival for those ineligible for transplant was 60% at 1 year (n=10)

CONCLUSIONS

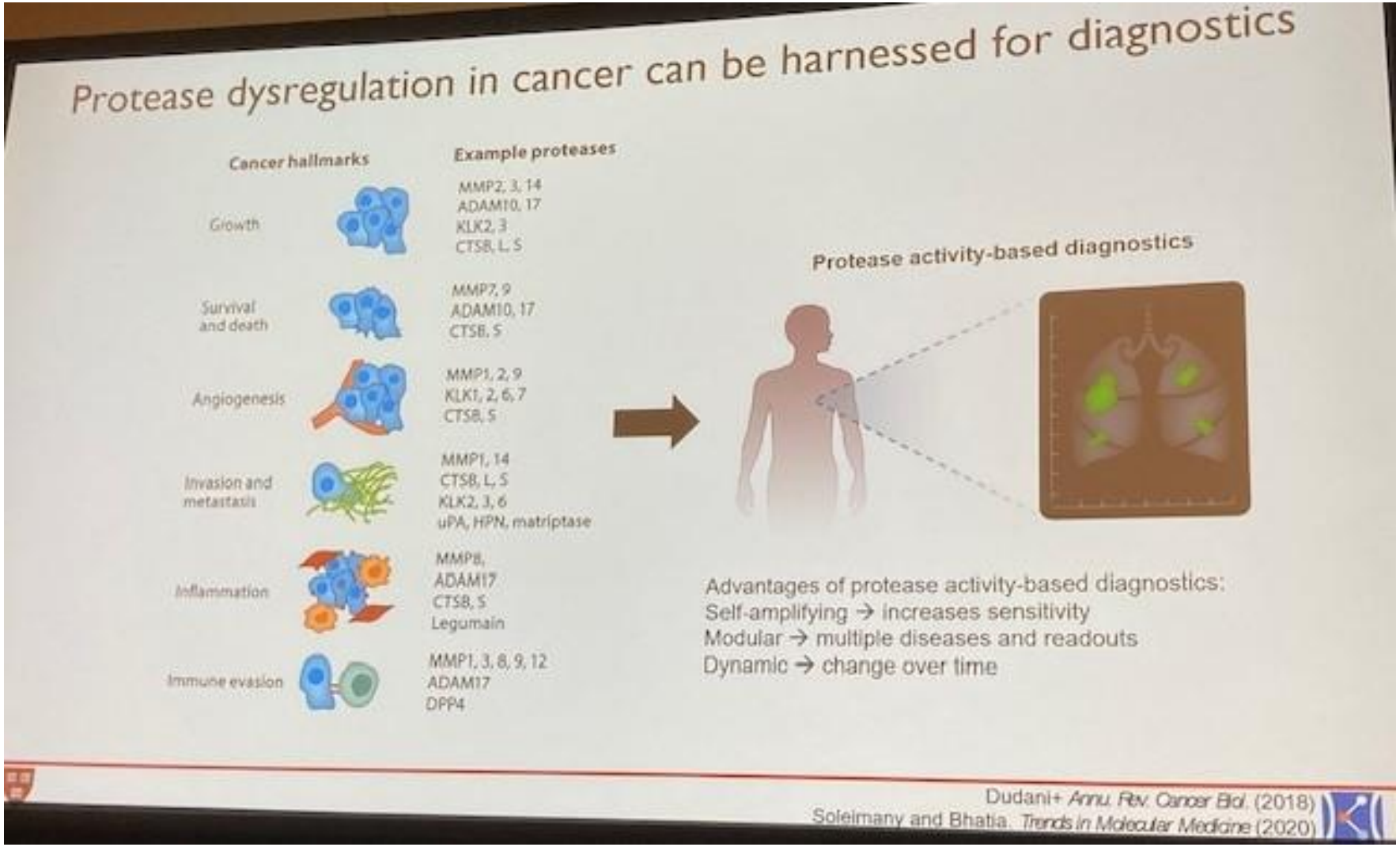
- It is important to streamline the appropriate imaging and procedura screening among patients referred for liver transplantation for CRLM
- There is a high rate of CRLM patients referred for Liver Transplantatio who do not progress to transplant during the lengthy evaluatio process
  - Most patients were ruled out due to extra-hepatic disease
- **CT chest, PET/CT imaging, and lymphadenectomy** appear essential t understanding why many do not progress to transplantation

DETECTION OF CHOLANGIOCARCINOMA WITH PROTEASE ACTIVITY PROBES

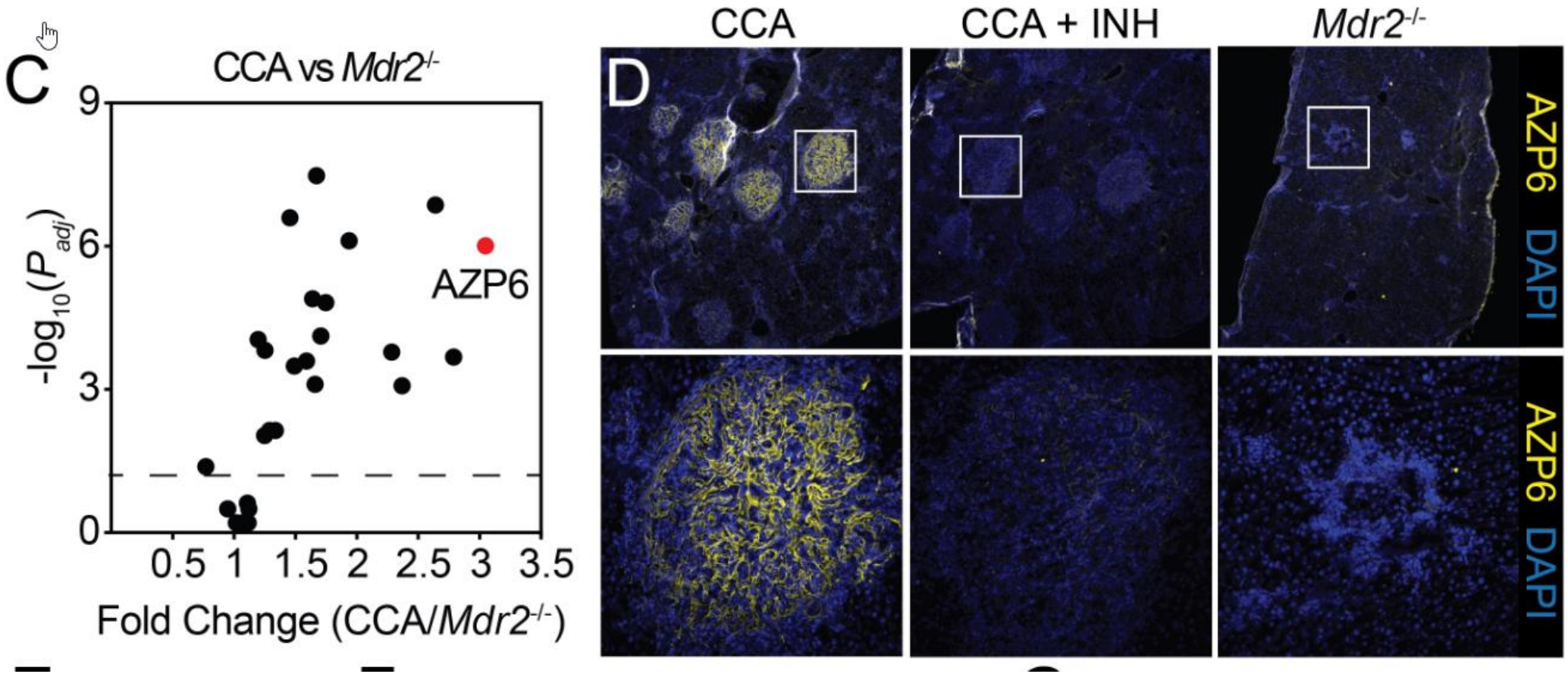
Background: Unfortunately, MRCP findings are nonspecific for CCA in the setting of biliary fibrosis and screening may not confer a survival benefit. We have previously developed a new class of diagnostic tools that detect dysregulated protease activity in the tumor microenvironment. In this work, we sought to leverage one such tool, activatable zymography probes (AZPs), which enable visualization of tumor-associated protease dysregulation *ex vivo* and *in vivo*. Because proteases have been shown to be dysregulated in CCA, we set out to develop a protease activity-based diagnostic for PSC-associated CCA.

Kirckpatrick J et al

DETECTION OF CHOLANGIOCARCINOMA WITH PROTEASE ACTIVITY PROBES



Kirckpatrick J et al



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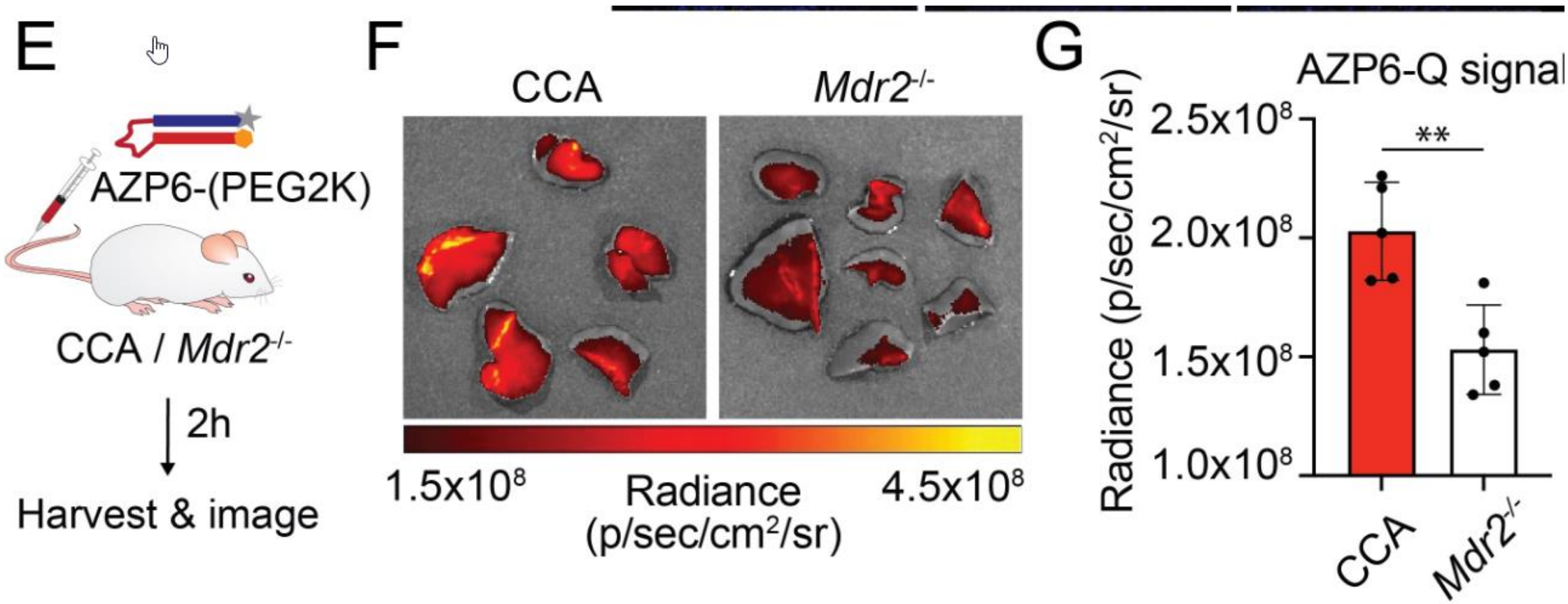

Kirckpatrick J et al

- **Conclusion:** AZPs detect and localize dysregulated protease activity *ex vivo* and *in vivo* in mouse models of CCA, without false positives from benign biliary fibrosis. Protease-activated diagnostics like AZPs, when used in conjunction with existing screening tools, may enable earlier and more accurate detection of CCA in PSC.

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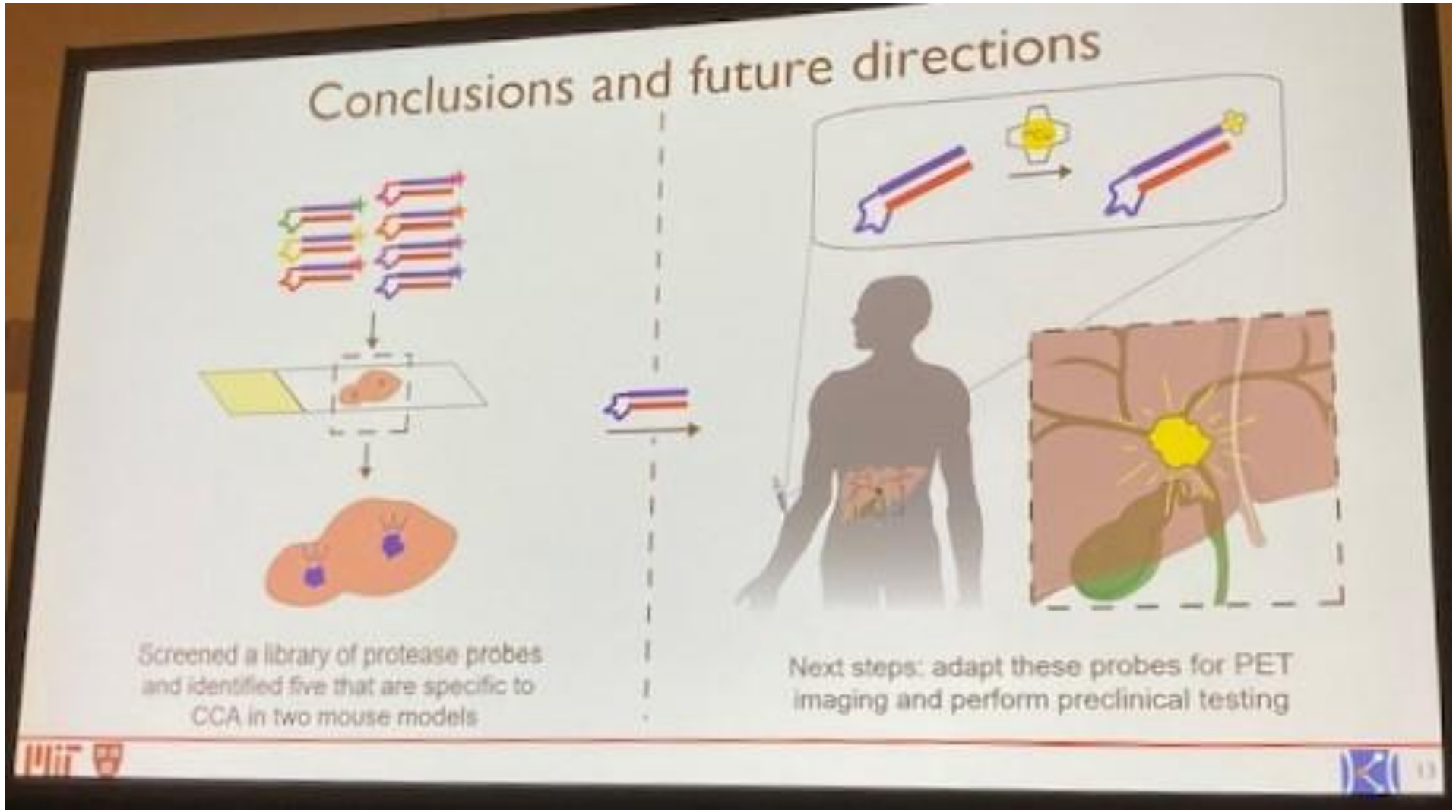

Korneck M et al

A NOVEL 5-POINT SCORING SYSTEM FOR THE DIFFERENTIATION OF HCC FROM INTRAHEPATIC CCA IN LR-M PATIENTS

- **Background:**
- Despite recent developments, it is still very difficult to differentiate hepatocellular carcinoma (HCC) from intrahepatic cholangiocarcinoma (iCCA).
- Here, we used the surface analysis interferometric and fluorescence imaging methodology for small extracellular vesicles (small EVs) analysis in liver cancer category (LI-RADS) M (LR-M) patients. We evaluated their clinical performance and proposed a 5-point system using serological markers to distinguish HCC from iCCA.

Korneck M et al

A NOVEL 5-POINT SCORING SYSTEM FOR THE DIFFERENTIATION OF HCC FROM INTRAHEPATIC CCA IN LR-M PATIENTS

- **Results:**
- 1) Whole sera particle concentrations isolated from iCCA and HCC differ significantly (p=0.0364) with a mean particle concentration/mL ± SD of $1.8x10^{15}$ ± $1.4x10^{15}$in iCCA and $8.2x10^{14}$ ± $5.3x10^{14}$ in HCC (AUROC 0.74, sensitivity and specificity 75% and 58.3%, respectively.
- 2) Individual small EV subpopulations were significantly elevated in iCCA ($CD9^+C133/2^+$: p=0.0315, AUROC 0.74 and $CD81^+CD133/2^+$: p=0.0244, AUROC 0.826).
- 3) Thrombocytes, ALP and CRP were elevated in iCCA compared to HCC. (p=0.0238 and AUROC 0.76; p=0.0023 and AUROC 0.85; p=0.0092 and AUROC 0.88, respectively).

Korneck M et al

A NOVEL 5-POINT SCORING SYSTEM FOR THE DIFFERENTIATION OF HCC FROM INTRAHEPATIC CCA IN LR-M PATIENTS

- On an individual basis, each biomarker such as particles, small EVs, thrombocytes, ALP, and CRP did not achieve sensitivity or specificity greater than 80%. However, when each biomarker was converted into a binary categorical variable and a final score was calculated by assigning a point for each factor to the biomarkers cut-off value below it, samples could be scored from 0 to 5. Samples with a score of 3 to 5 were categorized as HCC and 0 to 2 points as iCCA, resulting in a diagnostic performance with a sensitivity of 100% and a specificity of 83.3%.
- **Conclusion:**
- Our findings suppose that combining small EVs with serological biomarkers could improve the diagnostic performance of liquid biopsy markers in a clinical context.

Korneck M et al

TREATMENT WITH GEMCITABINE/CISPLATIN AND DURVALUMAB FOR BILIARY TRACT CANCER – FIRST REAL-WORLD DATA FROM A GERMAN PATIENT COHORT

Florian Gerhardt[1], Christian Müller[2], Jack Chater[3], Aaron Schindler[1], Sebastian Ebel[4], Marino Venerito[2], Udo Lindig[5], Raphael Mohr[6], Mara Egerer[6], Maik Schwarz[7], Thomas Berg[1] and Florian Van Bömmel[1]

[1]Division of Hepatology, Department of Medicine II, Leipzig University Medical Center, Leipzig, Germany [2]Department of Gastroenterology, Hepatology and Infectious Diseases, Otto von Guericke University Hospital, Magdeburg, Germany [3]Medical Clinic III, Klinikum Chemnitz, Chemnitz, Germany [4]Department of Diagnostic and Interventional Radiology, Leipzig University Medical Center, Leipzig, Germany [5]Medical Clinic II, University Hospital Jena, Jena, Germany [6]Department of Hepatology & Gastroenterology, Charité University Medicine Berlin, Berlin, Germany [7]MVZ Schöneck, Schöneck, Germany

Background

- Biliary tract cancer (BTC) is a rare and heterogenous disease with poor prognosis.
- Based on the results of the TOPAZ-1 trial, the combination therapy of gemcitabine and cisplatin with the immune checkpoint inhibitor durvalumab (GC+D) has recently been approved in Europe and in the US for the treatment of BTC.
- However, the role of this treatment outside of clinical studies has not yet been studied.
- Our aim was to study the tolerability and efficacy of GC+D in real-world patients.

Methods

We retrospectively included patients treated with GC+D in 6 German medical centers.

Before approval of durvalumab, patients were treated based on cost approval by the their health insurance.

Response was defined by RECIST1.1 criteria based on tomography on a 12 weekly basis.

Adverse events were categorized by CTCAE 5.0.

Abbreviations:
GC + D=gemcitabine and cisplatin and durvalumab
RECIST1.1= Response Evaluation Criteria In Solid Tumors
CTCAE 5.0.= Common Terminology Criteria of Adverse Events
ECOG=Eastern Cooperative Oncology Group

Table 1: Baseline characteristics of ithe included patients.

Characteristic	n
Age group	
<70 years	56
70-75 years	15
76-80 years	5
>80 years	3
Sex (male/female)	36/43
Liver cirrhosis	5
HBV infection	0
HCV infection	2
Primary tumor type	
intrahepatic	46
extrahepatic	23
gallbladder	10
Previous treatment	
surgery	17
radiotherapy	4
other	16
ECOG status	
0	41
1	34
2	4

Results

Patient baseline characteristics

A total of 79 patients were treated with GC+D in 6 participating medical centers between August 2022 and October 2023 (**Table 1**).

Duration and efficacy of GCD treatment

The mean survival of GC+D treatment was 33 weeks. 14 patients died during treatment (**Table 2, Figure 1**).

Table 2: Duration and efficacy of GC+D treatment. *mean ± SD [range]	
Duration GC+D (weeks)*	28 ± 20 [4-139]
Cycles GC+D (n)*	5.4 ± 2.8 [1-12]
Overall survival (weeks)*	32.6 ± 23 [8-183]
Dead (%)	14 (18%)
Following therapy line (%)	24 (30%)
Response at last follow-up (n)	
progressive disease	27
stable disease	20
partial response	9
complete response	2
missing	21

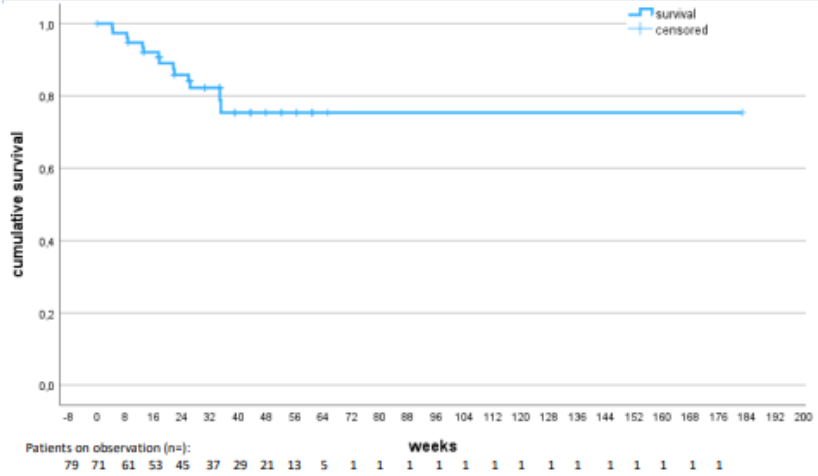

Figure 1: Kaplan-Meier analysis of overall survival during GC+D treatment.

Safety and Tolerability of GC+D treatment

Treatment with GC+D was generally well tolerated. Grade 3/4 adverse events occurred in 13 patients and included anemia, thrombocytopenia and neutropenia **(Table 3)**. 7 patients had to stop treatment due to side effects. However, immune-mediated side effects did not occur.

Table 3: Adverse Events during GC+D. (CTCAE 5.0)	
Grade I + II	**n**
anemia	17
thrombocytopenia	10
neutropenia	7
other	32
Grade III + IV	**n**
anemia	2
thrombocytopenia	4
neutropenia	7
other	0

Discussion

- Treatment with gemcitabine and cisplatin and durvalumab did not lead to immune mediated side effects.

- Longer follow up and larger patient populations are needed to define the real-world efficacy and tolerability of GC+D in the treatment of BTCs.