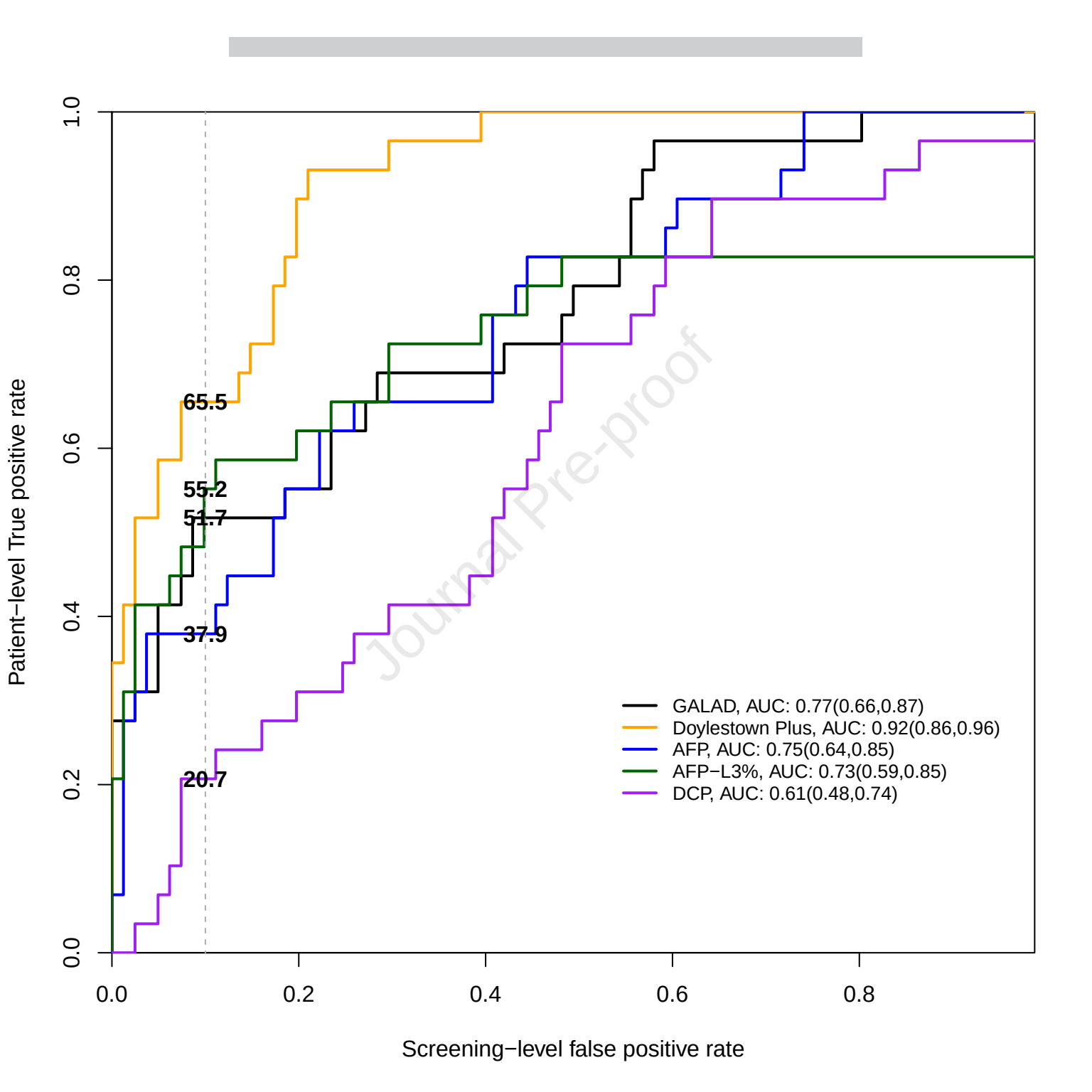
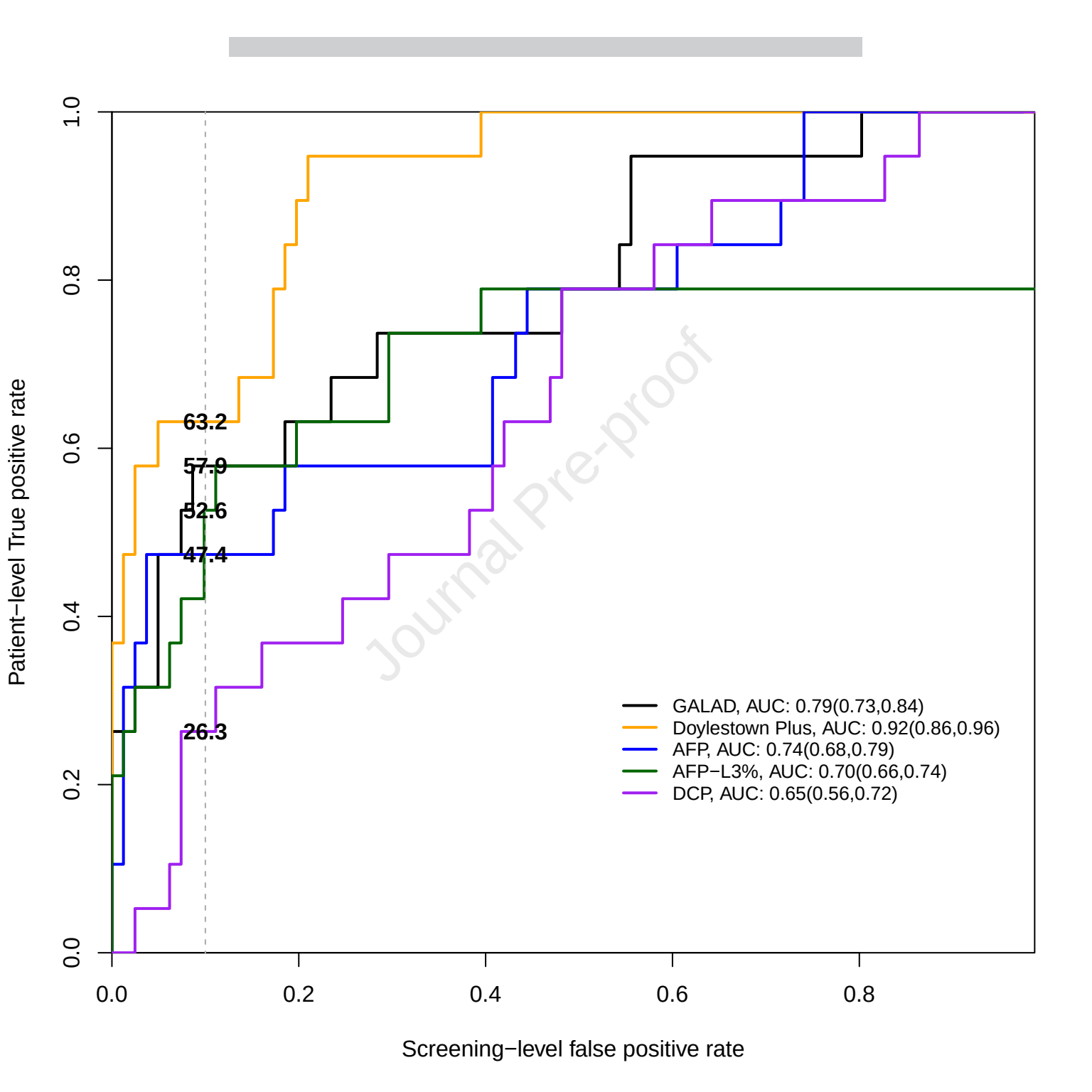

Patient−level True positive rate
Screening−level false positive rate
0.0
0.2
0.4
0.6
0.8
1.0
65.5
55.2
51.7
37.9
20.7
GALAD, AUC: 0.77(0.66,0.87)
Doylestown Plus, AUC: 0.92(0.86,0.96)
AFP, AUC: 0.75(0.64,0.85)
AFP−L3%, AUC: 0.73(0.59,0.85)
DCP, AUC: 0.61(0.48,0.74)
Journal Pre-proof


Patient−level True positive rate
Screening−level false positive rate
0.0
0.2
0.4
0.6
0.8
1.0
63.2
57.9
52.6
47.4
26.3
GALAD, AUC: 0.79(0.73,0.84)
Doylestown Plus, AUC: 0.92(0.86,0.96)
AFP, AUC: 0.74(0.68,0.79)
AFP−L3%, AUC: 0.70(0.66,0.74)
DCP, AUC: 0.65(0.56,0.72)
Journal Pre-proof

Supplemental Figure 1A: Receiver operating characteristic curves where patient-level sensitivity is estimated for any-stage HCC diagnosis

Supplemental Figure 1B: Receiver operating characteristic curves where patient-level sensitivity is estimated for early-stage HCC diagnosis

Supplemental material

Patients were excluded if they had known HCC or suspicious liver lesions, refractory ascites, grade 3-4 encephalopathy, hepatorenal syndrome, co-morbid medical conditions with a life expectancy of less than one year, prior solid organ transplant, or known extrahepatic primary tumor.

Serum was transferred to Wako Diagnostics lab for AFP, highly sensitive AFP-L3% and DCP measurements using a microchip capillary electrophoresis and liquid-phase binding assay on a μTASWako i30 auto analyzer (Wako Pure Chemical Industries, Ltd. Osaka, Japan). Serum was analyzed for fucosylated kininogen and PEG-precipitated IgG as previously described.[1]

GALAD was calculated using the equation: Z = -10.08 + (0.09 x age) + (1.67 x male sex) + (2.34 * log AFP) + (0.04 x AFP-L3) + (1.33 x log DCP). The Doylestown Plus algorithm was calculated using the equation: 1 / (1+EXP(-(-22.2602 + (0.1648*age) + (3.2923*$\log_{10}$ AFP) + (1.8921*PEG-precipitated IgG) + (0.3924*fucosylated kininogen)).

Supplemental References

1. Wang M, Shen J, Herrera H, Singal A, et al. *Biomarker analysis of fucosylated kininogen through depletion of lectin reactive heterophilic antibodies in hepatocellular carcinoma.* J Immunol Methods, 2018. **462**: p. 59-64.

Supplemental Table 1. Patient Characteristics

Characteristic	Cirrhosis controls (n=58)	HCC cases (n=29)	p-value
Age (median, 95%CI)	51.5 (27.0– 76.0)	53.0 (44.0 – 67.0)	0.3
Sex (% male)	32 (55.2%)	21 (72.4%)	0.2
Race/Ethnicity (%)			0.6
Non-Hispanic White	51 (87.9%)	25 (86.2%)	
Non-Hispanic Black	0	1 (3.4%)	
Hispanic White	2 (3.4%)	2 (6.9%)	
Asian	3 (5.2%)	1 (3.4%)	
Other/unknown	2(3.4%)	0	
Etiology of Liver Disease (%)			0.7
Hepatitis C	32 (55.2%)	18(62.1%)	
Alcohol-related	10(17.2%)	5(17.2%)	
Cryptogenic/NAFLD	6(10.3%)	4(13.8%)	
Hepatitis B	4(6.9%)	0(0%)	
Other	6(10.3%)	2(6.9%)	
Child Pugh Class (% Child A)	20 (34.5%)	9 (31.0%)	0.8
MELD	10 (6 – 17)	10 (6 – 17)	1.0
Number of HCC lesions			NA
1	N/A	20 (69.0%)	
2		6 (20.7%)	
4		1 (3.4%)	
>4		2 (6.9%)	
Maximum HCC diameter	N/A	2.6 (0.5 – 6.0)	NA
Vascular invasion or distant metastases	N/A	5 (17.2%)	NA
BCLC Stage			NA
Stage 0/A	N/A	17 (58.6%)	
Stage B		4 (13.8%)	
Stage C		2 (6.9%)	
Stage D		6 (20.7%)	

*Wilcoxon rank-sum tests were used to compare continuous variables and Fisher's exact test/Chi-squared test was used to compare categorical variables.