Supplementary materials

An individual patient data meta-analysis to determine cut-offs for and confounders of NAFLD-fibrosis staging with magnetic resonance elastography

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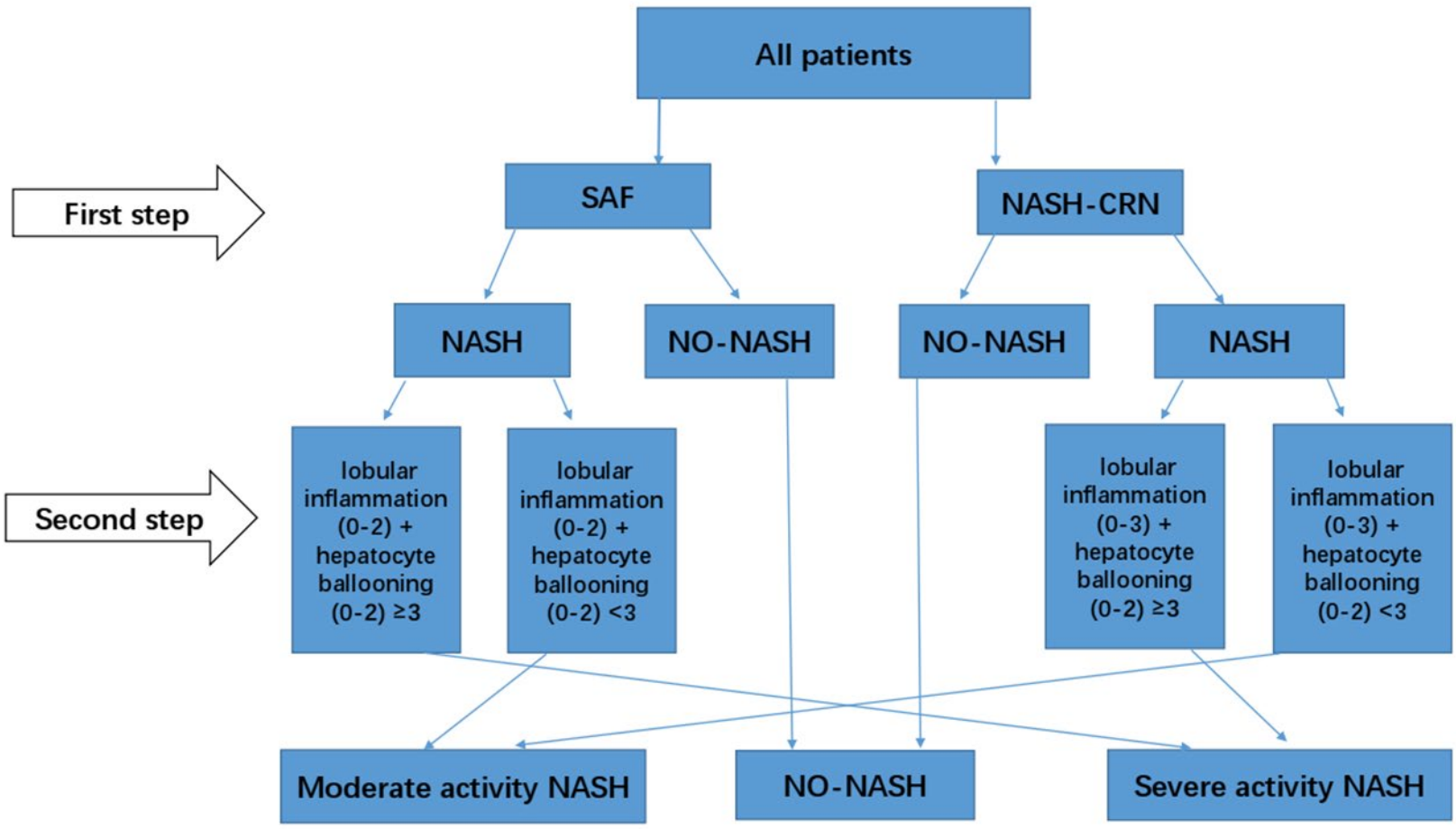
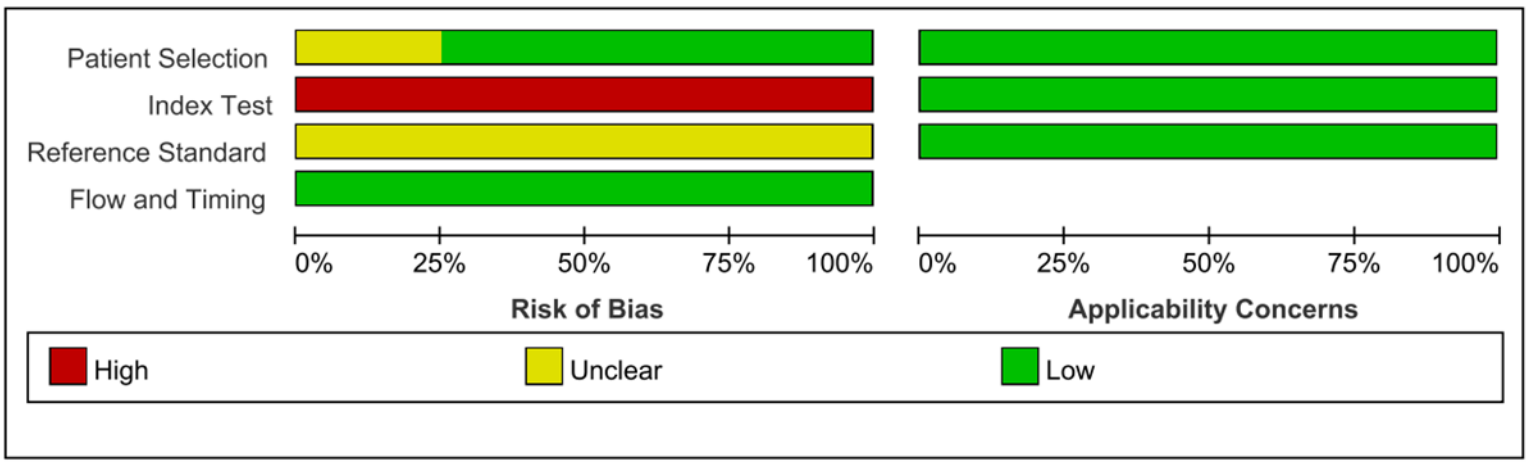
Fig. S1. NASH classification flow chart



NASH=Non-alcoholic steatohepatitis; MMA= Mild-moderate activity; SA=Severe activity; SAF= steatosis-activity-fibrosis histological scoring system; NASH-CRN= Nonalcoholic Steatohepatitis Clinical Research Network histologic.

Fig. S2a and b. Quality assessment with QUADAS-2 criteria.

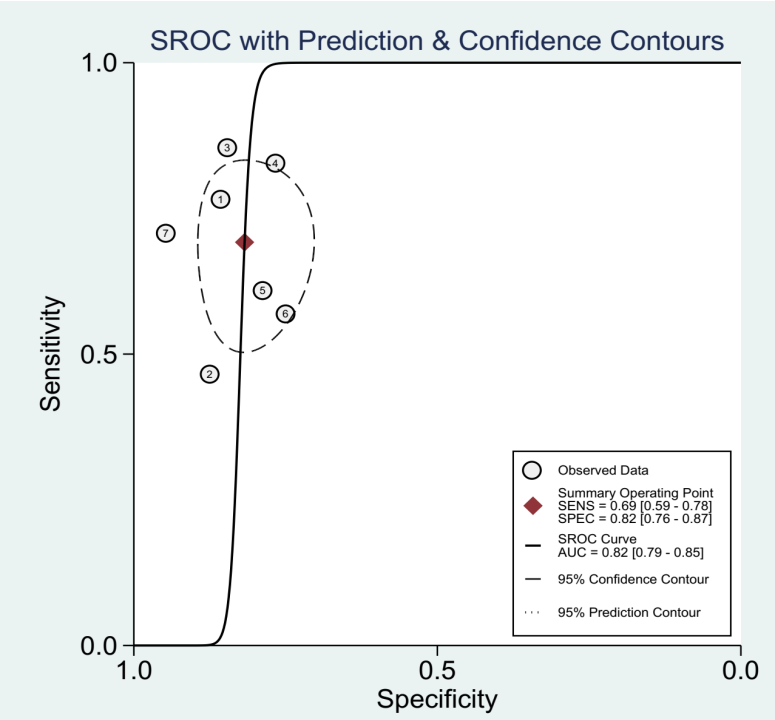
a.



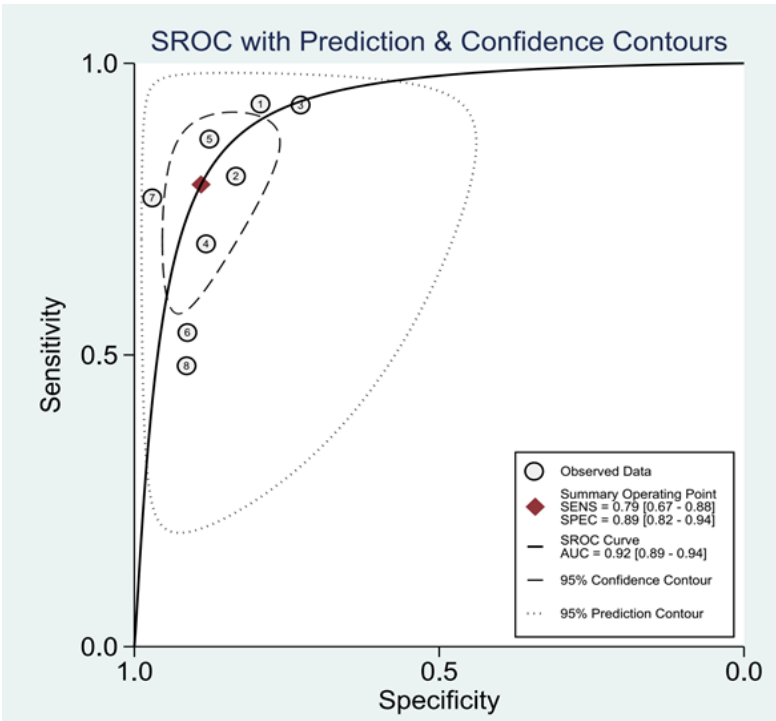
b.

Fig. S3 a.b.c.d The SROC curve of MRE for diagnosing different fibrosis stages

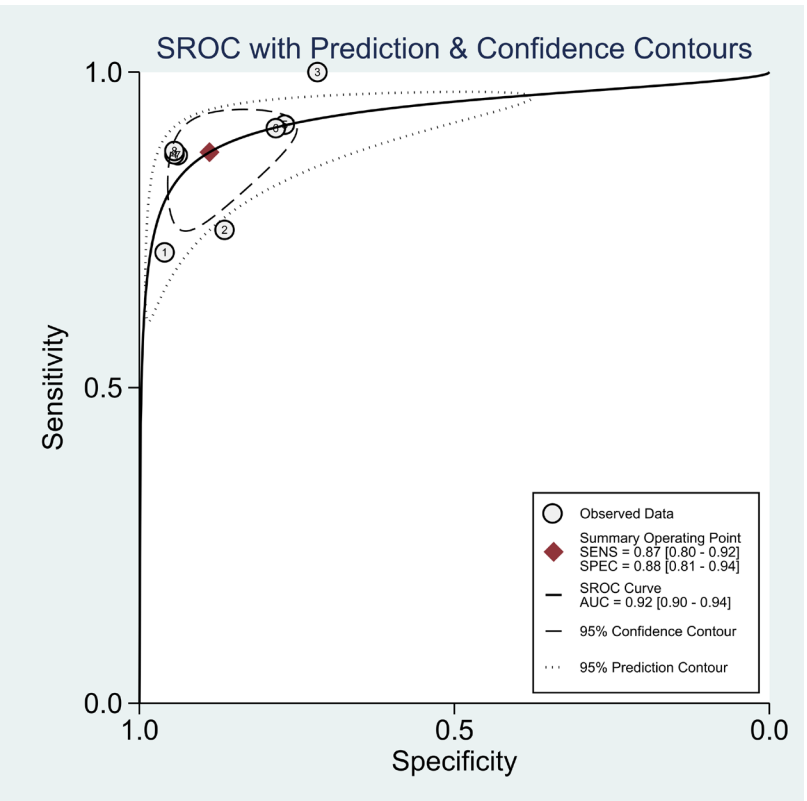
(Bivariate random-effects model. Figures were generated using Stata software v16 (Stata Corporation), *midas* package).



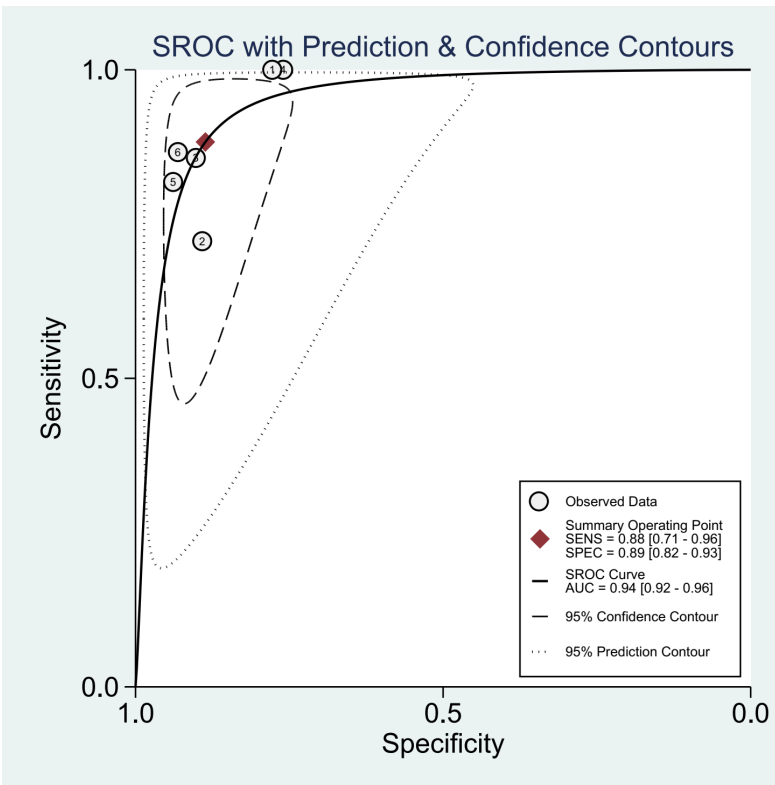
a. SROC curve for fibrosis stage F ≥ 1



b. SROC curve for fibrosis stage F ≥ 2



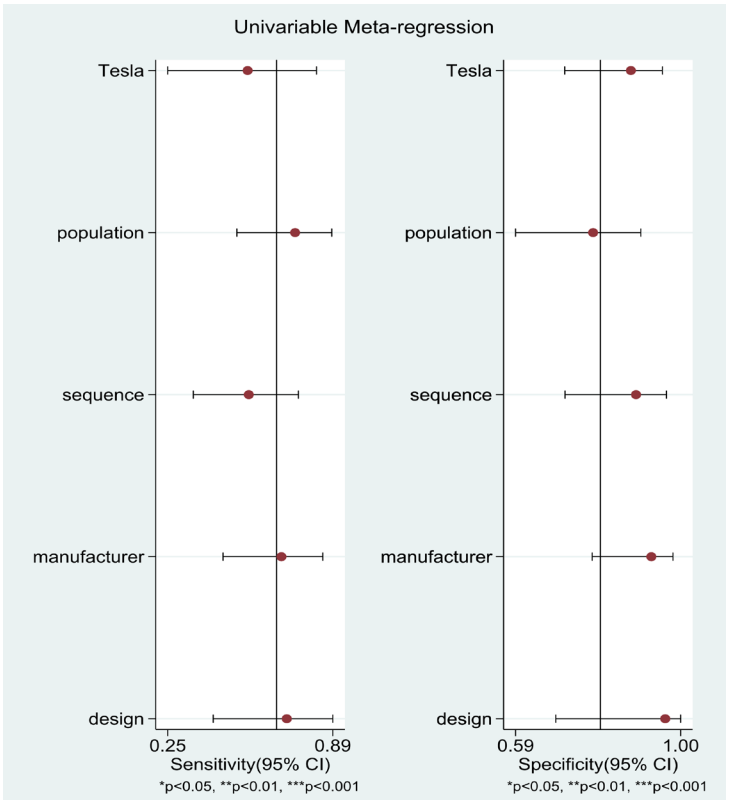
c. SROC curve for fibrosis stage F ≥ 3



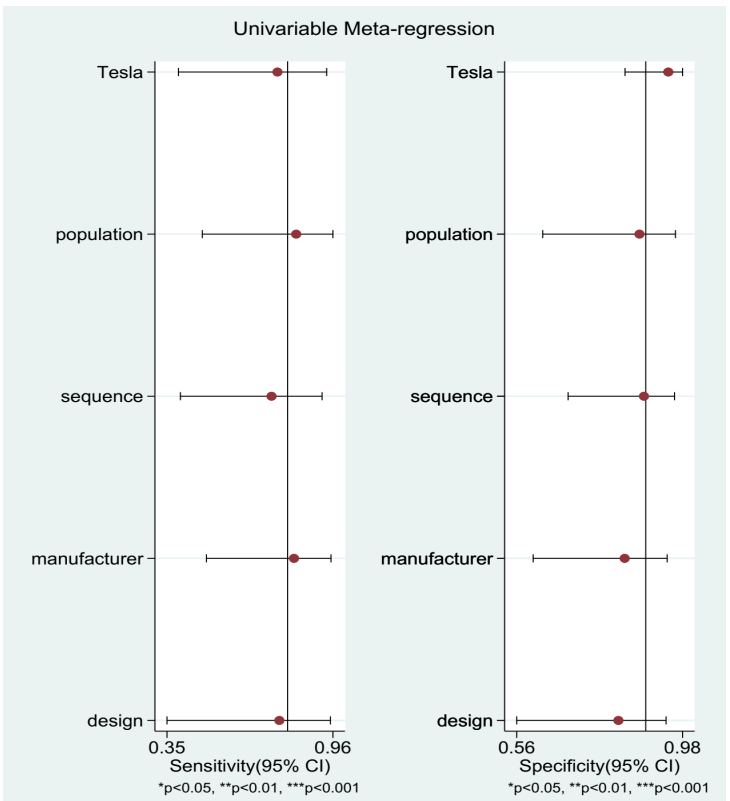
d. SROC curve for fibrosis stage F4

Fig. S4a.b.c.d. Univariable Meta-regression in staging different fibrosis stages.

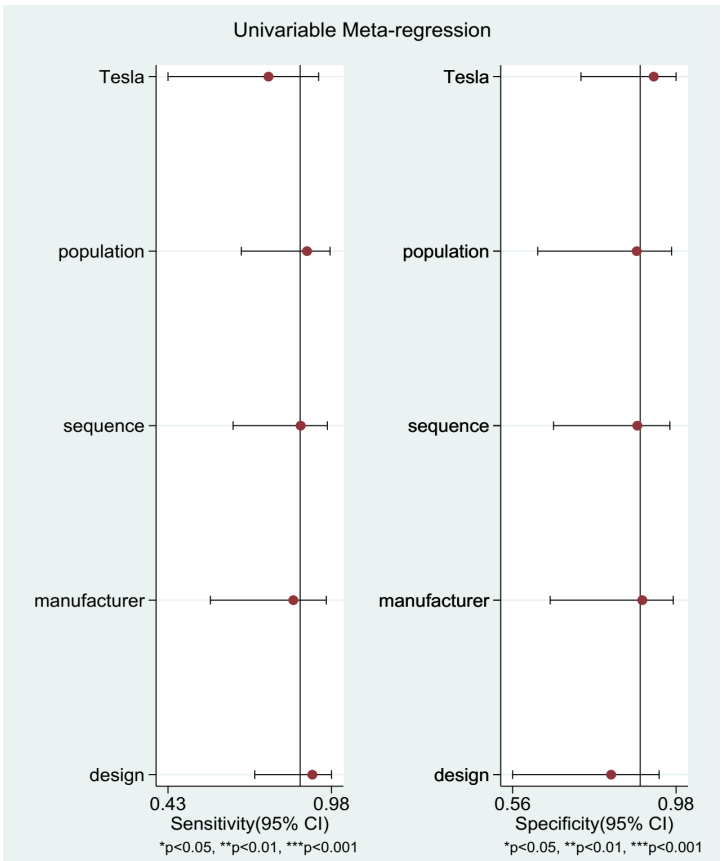
(Bivariate random-effects model. Figures were generated using Stata software v16 (Stata Corporation), *midas* package)



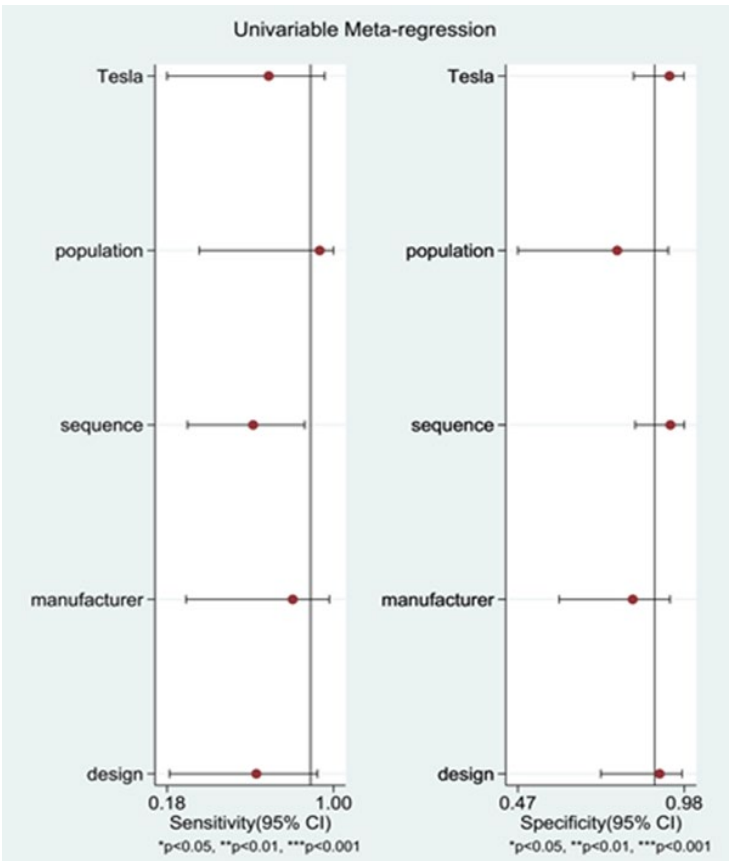
a. Meta-regression results of sensitivity and Specificity for fibrosis stage F ≥ 1;



b. Meta-regression results of sensitivity and specificity for fibrosis stage F ≥2;

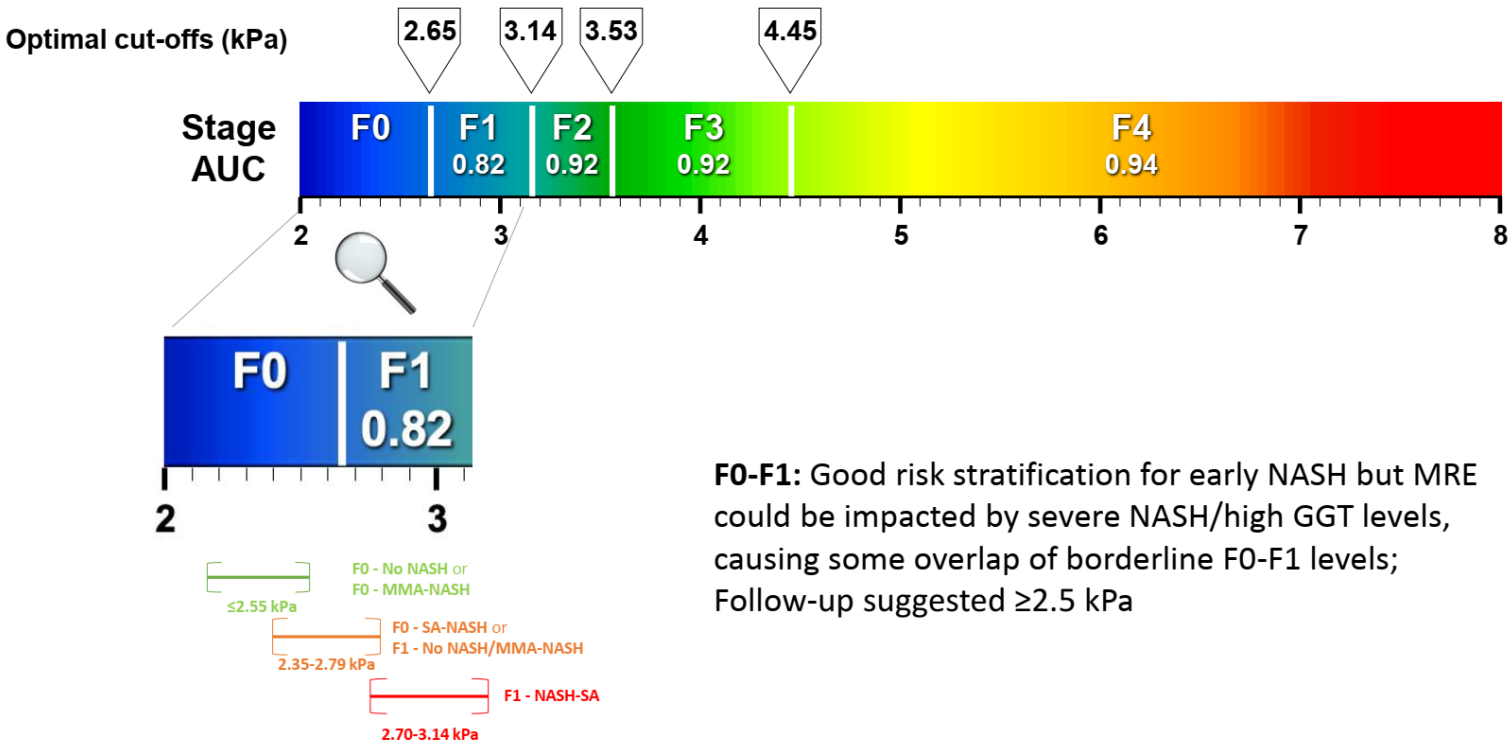


c. Meta-regression results of sensitivity and specificity for fibrosis stage F ≥ 3;



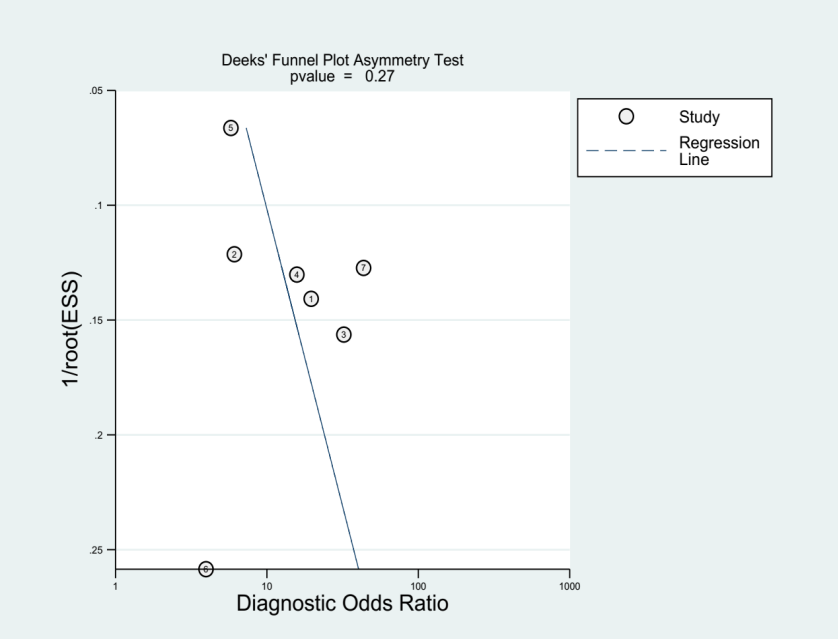
d. Meta-regression results of sensitivity and specificity for fibrosis stage F4;

Fig. S5. The LSM ranges of NASH with different activity degrees in the F0-1 stages

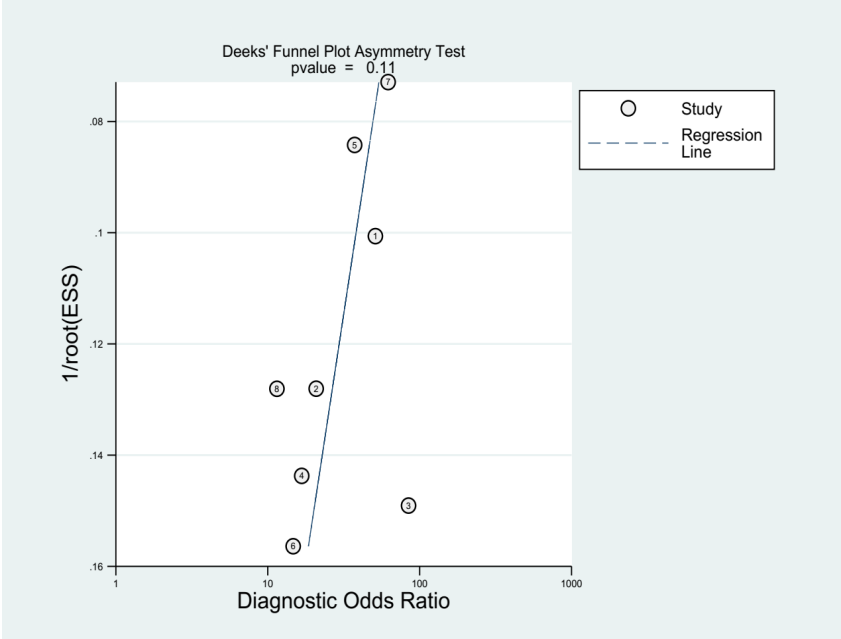


LSM (kPa) was shown as mean [95% CI], NASH=Non-alcoholic steatohepatitis; MMA= Mild-moderate activity; SA=Severe activity; LSM=liver stiffness measurement

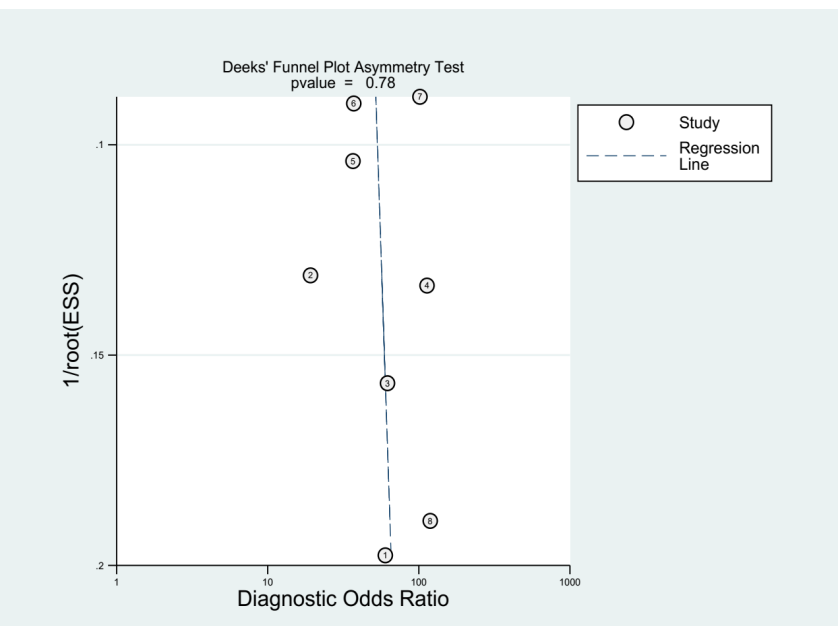
Fig. S6a.b.c.d. Deeks' funnel test for publication bias. (Bivariate random-effects model. Figures were generated using Stata software v16 (Stata Corporation), *midas* package)



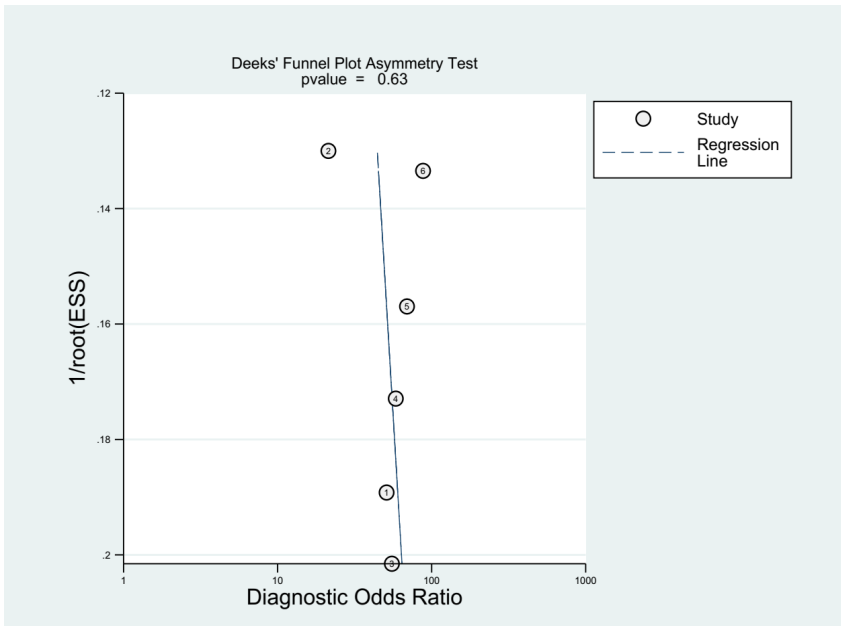
a. ≥F1



b. ≥ F2



c. ≥ F3



d. F4

Table S1. Subgroup and sensitivity analysis of the diagnostic accuracy of MRE in staging liver fibrosis.

(Delong method, Levels of significance: p<0.05)

	non-NASH	**NASH**	P value	**ATH (no)**	**ATH (yes)**	P value
≥F1	0.82[0.77-0.86]	0.79[0.74-0.83]	0.37	0.80[0.75-0.84]	0.79[0.73-0.85]	0.92
≥F2	0.93[0.90-0.96]	0.87[0.83-0.90]	<0.01	0.88[0.83-0.91]	0.87[0.82-0.92]	0.96
≥F3	0.96[0.93-0.98]	0.90[0.87-0.93]	<0.01	0.93[0.89-0.95]	0.87[0.82-0.92]	0.09
F4	0.92[0.88-0.95]	0.93[0.90-0.95]	0.63	0.92[0.89-0.95]	0.88[0.83-0.93]	0.27
	BMI<30 kg/m²	**BMI>30 kg/m²**	P value	**Steatosis（0-1）**	**Steatosis（2-3）**	P value
≥F1	0.81[0.76-0.85]	0.82[0.77-0.85]	0.83	0.81[0.76-0.84]	0.80[0.76-0.84]	0.96
≥F2	0.90[0.87-0.93]	0.89[0.86-0.92]	0.75	0.90[0.87-0.93]	0.88[0.85-0.91]	0.43
≥F3	0.93[0.89-0.95]	0.92[0.89-0.94]	0.69	0.93[0.90-0.96]	0.91[0.88-0.94]	0.25
F4	0.92[0.89-0.95]	0.88[0.83-0.93]	0.26	0.91[0.88-0.94]	0.94[0.91-0.96]	0.18
	Sex=F	**Sex=M**	P value	**T2DM(No)**	**T2DM(Yes)**	P value
≥F1	0.81[0.77-0.85]	0.77[0.73-0.82]	0.21	0.75[0.70-0.79]	0.86[0.82-0.90]	<0.01
≥F2	0.92[0.89-0.98]	0.89[0.85-0.93]	0.28	0.89[0.86-0.92]	0.88[0.84-0.91]	0.66
≥F3	0.92[0.89-0.94]	0.93[0.89-0.95]	0.75	0.94[0.91-0.96]	0.91[0.87-0.94]	0.21
F4	0.92[0.89-0.94]	0.94[0.91-0.96]	0.37	0.95[0.93-0.97]	0.90[0.86-0.94]	0.06
	GE	**Siemens/Philips**	P value	**Tesla 1.5T**	**Tesla 3.0T**	P value
≥F1	0.81[0.77-0.84]	0.79[0.73-0.84]	0.69	0.79[0.68-0.84]	0.82[0.78-0.84]	0.49
≥F2	0.92[0.88-0.94]	0.89[0.84-0.92]	0.89	0.90[0.82-0.99]	0.88[0.83-0.93]	0.71
≥F3	0.92[0.88-0.95]	0.93[0.91-0.95]	0.32	0.91[0.85-0.96]	0.93[0.90-0.94]	0.69
F4	0.94[0.91-0.96]	0.91[0.87-0.94]	0.31	0.94[0.88-0.97]	0.92[0.90-0.94]	0.62
	Asian	**No-Asian**	P value	**GRE**	**SE-EPI**	P value
≥F1	0.79[0.73-0.84]	0.82[0.77-0.85]	0.60	0.82[0.78-0.86]	0.80[0.75-0.84]	0.39
≥F2	0.90[0.86-0.94]	0.88[0.85-0.91]	0.45	0.91[0.87-0.94]	0.88[0.85-0.92]	0.54
≥F3	0.92[0.87-0.95]	0.93[0.91-0.96]	0.60	0.93[0.90-0.96]	0.92[0.89-0.94]	0.47
F4	0.95[0.92-0.98]	0.91[0.89-0.94]	0.28	0.94[0.91-0.96]	0.92[0.88-0.94]	0.26
	Sensitivity analysis					
	Interval between MRE and biopsy (<183days)		P value	**Interval between MRE and biopsy (<90 days)**	P value	
≥F1	0.80[0.76-0.83]		0.97	0.81[0.79-0.83]	0.60	
≥F2	0.89[0.87-0.91]		0.92	0.89[0.87-0.92]	0.92	
≥F3	0.92[0.90-0.94]		0.94	0.92[0.90-0.94]	0.97	
F4	0.92[0.90-0.94]		0.94	0.93[0.91-0.95]	0.59	
	R2*< 80 Hz	**All with R2***	P value			
≥F1	0.75[0.69-0.80]	0.75[0.69-0.80]	0.93			
≥F2	0.84[0.78-0.88]	0.83[0.78-0.88]	0.94			
≥F3	0.92[0.87-0.95]	0.92[0.88-0.95]	0.99			
F4	0.95[0.91-0.97]	0.95[0.91-0.97]	0.96			

BMI=Body mass index; NASH=Non-alcoholic steatohepatitis; T2DM= Type 2 diabetes mellitus; AHT=Arterial hypertension; GRE=Gradient-echo sequence; SE-EPI= Spin echo echo planar imaging.

Table S2. Comparison of diagnostic accuracy of 3 cut-off value systems (Singh 2016, Hsu2019 and our IPD meta-analysis) in the validation cohort (n=266). (Chi-square test was used to compare the accuracy between cut-off value systems. Levels of significance: p<0.05)

F0vsF1-F4 (208/58)	Cut-off(kPa)	Sensitivity(%)	Specificity(%)	YI	PLR	NLR	Accuracy(%)	P-value
Singh 2016	2.88	54[47-61]	83[71-91]	37	3.14[1.8 - 5.6]	0.55[0.5 - 0.7]	60[51-70]	0.51
Hsu 2019	2.61	64[58-71]	74[61-85]	38	2.50[1.6 - 3.9]	0.48[0.4 - 0.6]	66[56-76]	0.83
Current study 2022	2.65	62[55-69]	74[61-85]	36	2.41[1.5 - 3.8]	0.51[0.4 - 0.6]	64[55-75]	
F0-1VS F2-4(108/158)	**Cut-off(kPa)**	**Sensitivity(%)**	**Specificity(%)**	**YI**	**PLR**	**NLR**	**Accuracy(%)**	**P-value**
Singh 2016	3.54	58[49-68]	91[85-95]	49	6.14[3.7 - 10.2]	0.46[0.4 - 0.6]	78[68-89]	0.88
Hsu 2019	2.97	75[66-83]	79[82-85]	54	3.59[2.6 - 5.0]	0.32[0.2 - 0.4]	77[67-89]	0.84
Current study 2022	3.14	71[62-80]	84[77-89]	55	4.28[2.9 - 6.2]	0.35[0.3 - 0.5]	79[69-90]	
F0-2VS F3-4(64/202)	**Cut-off(kPa)**	**Sensitivity(%)**	**Specificity(%)**	**YI**	**PLR**	**NLR**	**Accuracy(%)**	**P-value**
Singh 2016	3.77	75[63-85]	89[84-93]	64	6.89[4.5 - 10.5]	0.28[0.2 - 0.4]	86[75-98]	0.85
Hsu 2019	3.62	78[66-88]	88[82-92]	66	6.31[4.3 - 9.3]	0.25[0.2 - 0.4]	86[75-98]	0.85
Current study 2022	3.53	78[66-88]	86[81-91]	64	5.64[3.9 - 8.1]	0.25[0.2 - 0.4]	84[76-96]	
F0-3VS F4 (21/245)	**Cut-off(kPa)**	**Sensitivity(%)**	**Specificity(%)**	**YI**	**PLR**	**NLR**	**Accuracy(%)**	**P-value**
Singh 2016	4.09	86[64-97]	83[78-87]	69	5.00[3.6 - 6.9]	0.17[0.06 - 0.5]	85[74-97]	0.71
Hsu 2019	4.69	71[48-89]	92[88-95]	63	9.21[5.5 - 15.3]	0.31[0.2 - 0.6]	90[79-100]	0.78
Current study 2022	4.45	76[53-92]	89[84-92]	65	6.67[4.4 - 10.2]	0.27[0.1 - 0.6]	88[77-99]	

PLR= Positive Likelihood Ratio; NLR=Negative Likelihood Ratio; YI= Youden Index; Accurary=(TP+TN)/All.

Table S3. Comparison of liver stiffness measurement by MRE with different GGT and NASH levels in each fibrosis stage (F0-F4). (Two-way ANOVA method, levels of significance: $p<0.05$)

F0 stage		**p-value**			**p-value**							**p-value**
GGT(IU/L)	**LSM(kPa)**	**<0.01**	**NASH**	**LSM(kPa)**	**<0.05**	**no-NASH*GGT(IU/L)**	**LSM(kPa)**	**MMA NASH*GGT(IU/L)**	**LSM(kpa)**	**SA NASH*GGT(IU/L)**	**LSM(kPa)**	**0.67**
<60	2.26[2.16-2.37]		**no-NASH**	2.23[2.14-2.32]		**no-NASH *GGT<60**	2.18[2.09-2.27]	**MMA NASH *GGT<60**	2.27[2.08-2.46]	**SA NASH *GGT<60**	2.35[2.09-2.60]	
60-120	2.23[2.02-2.45]		**NASH MMA**	2.37[2.18-2.55]		**no-NASH *60<GGT<120**	2.10[1.94-2.26]	**MMA NASH *60<GGT<120**	2.21[1.80-2.61]	**SA NASH *60<GGT<120**	2.39[1.92-3.87]	
>120	2.65[2.48-2.81]		**NASH SA**	2.55[2.35-2.76]		**no-NASH *GGT>120**	2.40[2.20-2.60]	**MMA NASH *GGT>120**	2.63[2.29-2.96]	**SA NASH *GGT>120**	2.92[2.61-3.23]	
F1 stage		**p-value**			**p-value**							**p-value**
GGT(IU/L)	**LSM(kPa)**	**<0.01**	**NASH**	**LSM(kPa)**	**<0.05**	**no-NASH *GGT(IU/L)**	**LSM(kPa)**	**MMA NASH*GGT(IU/L)**	**LSM(kPa)**	**SA NASH*GGT(IU/L)**	**LSM(kPa)**	**0.17**
<60	2.39[2.28-2.49]		**no-NASH**	2.62[2.45-2.79]		**no-NASH *GGT<60**	2.44[2.28-2.59]	**MMA NASH *GGT<60**	2.37[2.19-2.56]	**SA NASH *GGT<60**	2.36[2.14-2.57]	
60-120	2.65[2.50-2.81]		**NASH MMA**	2.56[2.39-2.73]		**no-NASH *60<GGT<120**	2.59[2.31-2.88]	**MMA NASH *60<GGT<120**	2.53[2.26-2.81]	**SA NASH *60<GGT<120**	2.84[2.61-3.06]	
>120	2.97[2.77-3.17]		**NASH SA**	2.83[2.70-2.97]		**no-NASH *GGT>120**	2.83[2.45-3.21]	**MMA NASH *GGT>120**	2.77[2.39-3.15]	**SA NASH *GGT>120**	3.30[3.03-3.57]	
F2 stage		**p-value**			**p-value**							**p-value**
GGT(IU/L)	**LSM(kPa)**	**0.30**	**NASH**	**LSM(kPa)**	**0.20**	**NASH*GGT(IU/L)**	**LSM(kPa)**	**MMA NASH*GGT(IU/L)**	**LSM(kPa)**	**SA NASH*GGT(IU/L)**	**LSM(kPa)**	**0.71**
<60	3.42[3.13-3.71]		**no-NASH**	3.14[2.64-3.64]		**no-NASH *GGT<60**	3.33[2.77-3.88]	**MMA NASH *GGT<60**	3.55[3.04-4.06]	**SA NASH *GGT<60**	3.39[2.96-3.82]	
60-120	3.20[2.79-3.61]		**NASH MMA**	3.51[3.10-3.92]		**no-NASH *60<GGT<120**	2.83[2.02-3.64]	**MMA NASH *60<GGT<120**	3.24[2.61-3.88]	**SA NASH *60<GGT<120**	3.53[2.87-4.19]	
>120	3.73[3.18-4.28]		**NASH SA**	3.70[3.35-4.06]		**no-NASH*GGT>120**	3.27[2.13-4.41]	**MMA NASH *GGT>120**	3.74[2.81-4.67]	**SA NASH *GGT>120**	4.19[3.47-4.91]	
F3-4 stage		**p-value**			**p-value**							**p-value**
GGT(IU/L)	**LSM(kPa)**	**0.38**	**NASH**	**LSM(kPa)**	**0.25**	**no-NASH *GGT(IU/L)**	**LSM(kPa)**	**MMA NASH*GGT(IU/L)**	**LSM(kPa)**	**SA NASH*GGT(IU/L)**	**LSM(kPa)**	**0.63**
<60	4.61[4.16-5.07]		**no-NASH**	5.14[4.70-5.57]		**no-NASH *GGT<60**	4.92[4.15-5.68]	**MMA NASH *GGT<60**	4.04[3.07-5.01]	**SA NASH *GGT<60**	4.88[4.28-5.47]	
60-120	5.02[4.51-5.54]		**NASH MMA**	4.58[3.82-5.33]		**no-NASH *60<GGT<120**	5.45[4.69-6.22]	**MMA NASH *60<GGT<120**	4.16[2.97-5.34]	**SA NASH *60<GGT<120**	5.46[4.81-6.10]	
>120	5.23[4.59-5.88]		**NASH SA**	5.15[4.80-5.50]		**no-NASH *GGT>120**	5.05[4.30-5.80]	**MMA NASH *GGT>120**	5.53[3.86-7.20]	**SA NASH *GGT>120**	5.12[4.54-5.71]	

LSM(Kpa) was shown as mean [95% CI]; GGT=gamma-glutamyl transferase; NASH=Non-alcoholic steatohepatitis; MMA= Mild-moderate activity; SA=Severe activity; LSM=liver stiffness measurement.

Table S4. Diagnostic performance of "Rule out" cut-off (at sensitivity of 90%) and "Rule in" cut-off (at specificity of 90%) for mild fibrosis (≥F1),significant fibrosis (≥F2),advanced fibrosi s(≥F3) and cirrhosis (F4). (ROC analysis method).

	Cut-off (kPa)	Sensitivity(95%CI)	Specificity(95%CI)	PLR(95%CI)	NLR(95%CI)	PPV(95%CI)	NPV(95%CI)
≥F1	**2.09 （Se=90）**	90.42[87.8 - 92.7]	36.45[29.8 - 43.5]	1.42[1.3 - 1.6]	0.26[0.2 - 0.4]	80.7[78.9 - 82.3]	56.5[48.9 - 63.8]
	2.91 （Sp=90）	54.96[50.9 - 59.0]	90.15[85.2 - 93.9]	5.58[3.7 - 8.5]	0.50[0.5 - 0.6]	94.2[91.5 - 96.1]	40.6[38.2 - 43.0]
≥F2	**2.50 （Se=90）**	90.38[86.6 - 93.4]	59.67[55.2 - 64.1]	2.24[2.0 - 2.5]	0.16[0.1 - 0.2]	59.3[55.7 - 62.9]	90.5[86.4 – 93.7]
	3.30 （Sp=90）	72.12[66.8 - 77.0]	89.92[86.9 - 92.4]	7.15[5.4 - 9.4]	0.31[0.3 - 0.4]	82.3[76.8 – 86.8]	83.2[80.1 – 86.1]
≥F3	**3.27 （Se=90）**	90.62[85.6 - 94.3]	82.18[78.9 - 85.1]	5.09[4.3 - 6.1]	0.11[0.07 - 0.2]	61.8[57.4 - 65.8]	96.5[94.7 - 97.7]
	3.74 （Sp=90）	77.08[70.5 - 82.8]	90.10[87.4 - 92.4]	7.79[6.0 - 10.0]	0.25[0.2 - 0.3]	71.2[65.7 - 76.0]	92.5[90.5 - 94.2]
F4	**3.78 （Se=90）**	90.14[80.7 - 95.9]	80.74[77.7 - 83.5]	4.68[4.0 - 5.5]	0.12[0.06 - 0.2]	31.4[27.9 - 35.1]	98.8[97.6 - 99.4]
	4.60 （Sp=90）	73.24[61.4 - 83.1]	89.96[87.5 - 92.0]	7.29[5.6 - 9.5]	0.30[0.2 - 0.4]	41.6[35.5 - 48.0]	97.2[95.9 - 98.1]

PLR= Positive Likelihood Ratio; NLR=Negative Likelihood Ratio; PPV=Positive Predictive Value; NPV= Negative Predictive Value.

Table S5. Impact of prevalence of F≥F2, ≥F3 and F=4 on positive predictive value (PPV) and negative predictive value (NPV) for cut-offs. (Bayes' theorem and ROC analysis method)

		Prevalence	**Pooled cut-off** **Cut-off=3.14**	**Rule out (Se=90)** **Cut-off=2.50**	**Rule in (Sp=90)** **Cut-off=3.30**
For significant fibrosis (≥F2)	Actual prevalence in our cohort	39.4%	PPV= 79.4[74.2 – 83.9] NPV=85.9[82.6 – 88.7]	PPV=59.3[55.7 – 62.9] NPV=90.5[86.4 – 93.7]	PPV=82.3[76.8 – 86.8] NPV=83.2[80.1 – 86.1]
	Estimated prevalence in diabetic clinic	40%	PPV=79.8[76.2 – 84.2] NPV=85.5[85.8 – 88.4]	PPV=59.9[56.3 – 63.4] NPV=90.3[86.1 – 93.6]	PPV=82.7[77.3 – 87.1] NPV=82.87[79.7 – 85.8]
	Estimated prevalence in general population	7%	PPV=30.8[26.5 – 37.6] NPV=98.1[98.2 - 98.5]	PPV=14.4[12.7 – 16.4] NPV=98.8[98.2 - 99.2]	PPV=35.0[27.7 – 43.3] NPV=97.7[97.2 - 98.2]
			Cut-off=3.53	**Cut-off=3.27**	**Cut-off=3.74**
For advanced fibrosis (≥F3)	Actual prevalence in our cohort	24.1%	PPV=66.9[60.4 – 72.7] NPV=94.1[91.9 – 95.9]	PPV=61.8[56.3 – 66.8] NPV=96.5[94.5 - 97.9]	PPV=71.2[64.0 – 77.6] NPV=92.5[90.3 - 94.4]
	Estimated prevalence in diabetic clinic	18%	PPV=58.2[51.3 – 64.8] NPV=95.8[94.3 – 97.1	PPV=52.8[47.1 – 58.2] NPV=97.6[96.5 – 98.6]	PPV=63.1 [55.1- 70.5] NPV=94.7[93.1 – 96.1]
	Estimated prevalence in general population	2%	PPV=11.5[8.9 – 14.6] NPV=99.6[99.4 - 99.7]	PPV= 9.4 [7.6 – 11.4] NPV=99.8[99.6 - 99.9]	PPV=13.7[10.2 – 18.2] NPV=99.5[99.3- 99.6]
			Cut-off=4.45	**Cut-off=3.78**	**Cut-off=4.6**
For cirrhosis (F4)	Actual prevalence in our cohort	8.7%	PPV=39.1[30.8 – 47.2] NPV=97.5[96.2 - 98.5]	PPV=30.8[25.6 – 35.6] NPV=98.9[97.7 - 99.5]	PPV=41.0[31.9 – 49.7] NPV=97.2[96.0 – 98.3]
	Estimated prevalence in diabetic clinic	3%	PPV=17.3[12.6 – 22.5] NPV=99.2[98.7 - 99.5]	PPV=12.6[10.1 – 15.2] NPV=99.6[99.2 - 99.9]	PPV=18.4[13.2 – 24.3] NPV=99.1[98.7 - 99.4]
	Estimated prevalence in general population	1%	PPV= 6.3 [4.5 – 8.7] NPV=99.7[99.6 – 99.8]	PPV=4.5[3.5 – 5.5] NPV=99.9[99.8 – 100]	PPV=6.8[4.7 – 9.5] NPV=99.7[99.6 – 99.8]