A NEW NON-INVASIVE DIAGNOSTIC SCORE TO MONITOR CHANGE IN DISEASE ACTIVITY AND PREDICT FIBROSIS EVOLUTION IN PATIENT WITH NASH

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BACKGROUND & AIMS

There is an urgent need for novel, non-invasive methods to diagnose NASH and monitor disease evolution.

We have previously reported composite algorithms (refered here as NIS6) including 6 variables (α2 macroglobulin, mir34a and mir200a in plasma, PIIINP, YKL-40 (CHI3L1), HbA1c) with good diagnostic performances to detect patients To-Be-Treated (NAS≥4;F≥2).

Using samples from GOLDEN-505 cohort and measuring serum levels of mir34a, a similar linear logistic regression approach has generated a simplified algorithm (refered here as NIS4) with 4 circulating variables (α2-macroglobulin, mir34a in serum, YKL-40 and HbA1c).

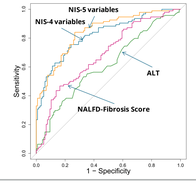
- The main objectives of this study were to:
  - Assess relationships of NIS4 with histological lesions at inclusion in GOLDEN-505.
  - Investigate the potential of NIS4 for the monitoring of histological changes at 1 year.

METHODS

- NASH patients (NAS≥3; ≥1 in steatosis, inflammation and ballooning) included in GOLDEN-505 trial (N=238).
- Circulating levels of miRNAs were measured in serum samples collected at inclusion (baseline) and 52 weeks after inclusion (week52).
- A linear logistic regression approach was used on the complete dataset to generate the best algorithm for identification of patients To-Be-Treated (TBT=NAS≥4; F≥2, N=104) at inclusion.
- The diagnostic value of this new non-invasive diagnostic score (NIS4) was investigated by:
  - ROC analyses of baseline NIS4 in detection of TBT patients at inclusion,
  - Correlations of baseline NIS4 with baseline histological scores. For this analysis, patients were grouped according to baseline histological scores including NAS, Activity Index (AI=Lobular inflammation + Ballooning score), steatosis score and NASH-CRN-fibrosis stage.
- The potential of NIS4 to monitor disease evolution was investigated by:
  - Use of the second liver biopsy and corresponding samples collected at week52,
  - Correlations between change in NIS4 and change of histological scores at week52 vs baseline. For this analysis, patients were grouped according to histological score change (improvement, no-change, worsening).
- Value of baseline NIS4 to predict fibrosis evolution at week52 was assessed in TBT patients of the placebo group.

NIS4 DIAGNOSTIC PERFORMANCES

ROC curves for NIS4 and NIS6, NAFLD-Fibrosis Score and ALT for identification of TBT (NAS≥4, F≥2) in GOLDEN-505 cohort



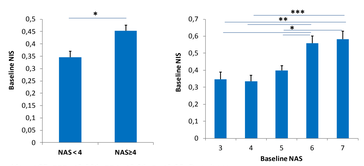
Comparison of performances of NIS4 vs other non-invasive scores for identification of TBT (NAS≥4, F≥2) vs NTBT in GOLDEN-505 cohort

Scores	AUC	Cut-off	Accuracy	Sensitivity	Specificity	PPV	NPV
NIS (4 variables)	**0.82**	**0.4255**	**75.94**	**73.12**	**78.15**	**72.34**	**78.81**
NIS (6 variables)	0.84	0.3502	77	84	72	70	85
NAFLD Fibrosis Score	0.69	0.676	34.12	66.67	8.47	36.47	24.39
ELF	0.70	7.7	45.28	97.28	4.20	44.39	71.43
FibroTest	0.68	0.48	66.51	40.86	86.55	70.37	65.19
Fibrometre S	0.73	0.62	64.15	32.26	89.08	69.77	62.72
BARD	0.64	2	59.91	60.22	59.66	53.85	65.74
APRI	0.72	1	66.51	26.88	97.48	89.29	63.04
FIB-4	0.72	3.25	58.96	6.45	100.00	100.00	57.77

- NIS4 and NIS6 had comparable diagnostic performances to identify TBT in GOLDEN-505 cohort. Both were more discriminating than other scores described in the literature.

CORRELATION OF BASELINE NIS4 WITH BASELINE HISTOLOGICAL SCORES

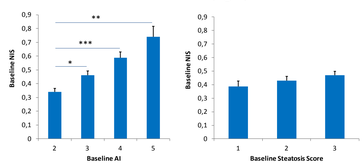
Baseline NIS4 vs baseline NAS in GOLDEN-505 cohort



*Mean±SE, ***p<0.001, **<p<0.01, *p<0.05, Dunn's test*

- Patients with NAS≥4 at incusion had significantly higher baseline NIS4 than patients with NAS<4.
- After grouping patients according to baseline NAS, there was a positive relationship between baseline NIS4 and baseline NAS.

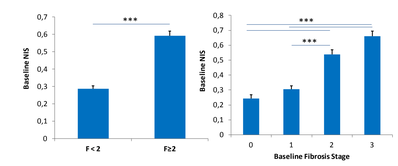
Baseline NIS4 vs baseline Activity Index (left) and baseline teatosis score (right) at inclusion



*Mean±SE, ***p<0.001, **<p<0.01, *p<0.05, Dunn's test*

- After grouping patients according to baseline AI or baseline steatosis scores, there was a positive relationship between baseline NIS4 and baseline Activity Index (hepatocyte ballooning + lobular inflammation) but not between baseline NIS4 and baseline steatosis score.

Baseline NIS4 vs baseline fibrosis stage at inclusion

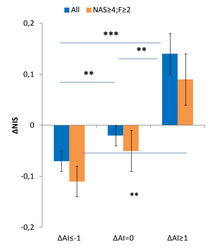


*Mean±SE, ***p<0.001, Dunn's test*

- Patients with F≥2 had significantly higher baseline NIS4 than patients with F<2.
- After grouping patients according to baseline fibrosis stage, there was a positive relationship between baseline NIS4 and baseline fibrosis stage.

CORRELATIONS OF NIS4 CHANGES WITH HISTOLOGICAL CHANGES (WEEK52 VS BASELINE)

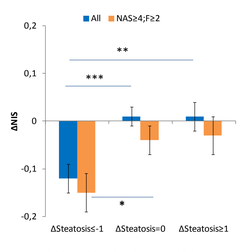
NIS4 changes (ΔNIS) in subgroups of patients with improved (ΔAI≤-1), stable (ΔAI=0) or worsened (ΔAI≥1) Activity Index at week52 vs baseline



*Mean±SE, ***p<0.001, **<p<0.01, Dunn's test*

- Patients showing ΔAI≤-1 had significantly higher hepatocyte ballooning score (p<0.01), lobular inflammation score (p<0.001) and NAS (p<0.05) at baseline than patients with ΔAI=0 or ΔAI≥1. In contrast, there was no significant difference in steatosis score and fibrosis stage at baseline (data not shown).
- There was a significant correlation between change in NIS4 and change of Activity Index (week52 vs baseline). Similar results were obtained when considering only patients with NAS≥4 and F≥2 at inclusion.

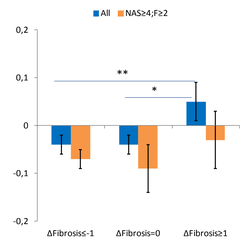
NIS4 changes (ΔNIS) in subgroups of patients with improved (ΔS≤-1), stable (ΔS=0) or worsened (ΔS≥1) steatosis score at week52 vs baseline



*Mean±SE, ***p<0.001, **<p<0.01, *p<0.05, Dunn's test*

- Patients showing ΔS≤-1 (N=123) had significantly higher steatosis score (p<0.001) and NAS (p<0.001) at baseline than patients with ΔS=0 (N=82) or ΔS≥1 (N=32). In contrast, there was no significant difference for hepatocyte ballooning and lobular inflammation scores and for fibrosis stage at baseline.
- NIS4 declined in patients with improvement in steatosis score (ΔS≤-1) while there was no change in patients with ΔS=0 or ΔS≥1. Similar results were obtained when considering only patients with NAS≥4 and F≥2 at baseline.

NIS4 changes (ΔNIS) in subgroups of patients with improved (ΔF≤-1), stable (ΔF=0) or worsened (ΔF≥1) fibrosis stage at week52 vs baseline

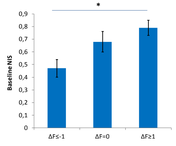


*Mean±SE, **<p<0.01, *p<0.05, Dunn's test*

- Patients showing ΔF≤-1 (N=87) had significantly higher fibrosis stage at baseline (p<0.001) than patients with ΔF=0 (N=101) or ΔF ≥1 (N=49). In contrast, there was no significant difference for all other histological scores at baseline.
- NIS4 similarly declined in patients with fibrosis improvement (ΔF≤-1) and in patients with stable fibrosis stage (ΔF=0) while NIS4 increased in patients with increasing fibrosis stage (ΔF≥1). In patients with NAS≥4 and F≥2, ΔNIS was not correlated with change in fibrosis stage.

PREDICTION OF FIBROSIS EVOLUTION

Baseline NIS4 vs fibrosis score evolution at week52 vs baseline



*Mean±SE, *p<0.05, Dunn's test*

- In patients with with NAS≥4 and F≥2 at inclusion and treated with placebo, those who showed improvement in fibrosis stage at week52 had significantly lower baseline NIS4 compared to patients who showed fibrosis worsening.

CONCLUSIONS

- **This study reports the diagnostic performance of a new non-invasive score combining circulating levels of four variables: α2-macroglobulin, mir34a, HbA1c and YKL-40 (CH3L1).**
- **Compared to existing scores, NIS4 can efficiently identify patients To-Be-Treated (NAS≥4; F≥2).**
- **The diagnostic performance of NIS4 is driven by correlations with Activity Index (necro-inflammation) and liver fibrosis stage at baseline. In contrast NIS4 does not correlate with steatosis score.**
- **Changes in NIS4 are correlated with changes in Activity Index with weaker correlations with change in steatosis and fibrosis stage.**
- **Together these results suggest that NIS4 holds promise for identification of patients To-Be-Treated and for monitoring disease activity.**
- **Diagnostic and disease monitoring performance of NIS4 should be further explored in independent longitudinal cohorts.**

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