Analysis of discrimination and calibration of two cardiovascular risk scores in patients with non-alcoholic steatohepatitis shows a need for improved accuracy of these models

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BACKGROUND

- Among NASH patients, the leading cause of mortality is cardiovascular disease/events[1-2]
- Cardiovascular (CV) risk is often estimated using two validated scoring algorithms:
  - Framingham algorithm for estimating the 10-year risk of clinical CVD[3]
  - Pooled Cohort Equations (PCE) for the 10-year risk of hard atherosclerotic cardiovascular disease (ASCVD)[4]
- Overestimation has been found in both the Framingham and PCE algorithms with rates of 51% and 78%, respectively[5]
- Framingham and PCE were tested on a NASH cohort (patients with increased morbidity and mortality from CVD) to assess their relevance

OBJECTIVE

- To assess the prognostic performance of the Framingham and PCE risk scores in a NAFLD/NASH real world cohort

METHODS

- Data were utilized from adult patients (≥18 years) enrolled in the US in TARGET-NASH and categorized into disease category (i.e. NAFLD, non-cirrhotic NASH, and cirrhotic NASH classified by biopsy if one was available or clinical criteria defined by Barritt et al[6])
- TARGET-NASH is a real-world longitudinal observational cohort of pediatric and adult patients receiving usual standard of care for NAFLD across the United States and Europe (ClinicalTrials.gov identifier, NCT02815891)
- Patients with a history of CV events at or prior to index were excluded
- Study populations for the Framingham and PCE were generated according to risk score requirements 5-year CV risk was estimated using recalibrated Framingham and PCE models and compared to observed CV events
- Model discrimination and calibration were assessed using the area under the receiver operator curve (AUROC) and Hosmer-Lemeshow test statistic, respectively

Table 1. Patient Demographics

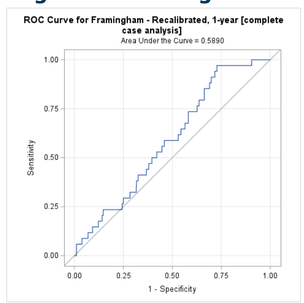
	Framingham[1] (n=980)	PCE[1] (n=587)
Age, median	56.0	57.0
Race		
White	80.1%	91.8%
Black	6.0%	8.2%
Other/not reported	13.9%	0%
Female	59.3%	62.5%
Site Type		
Academic	65.8%	65.4%
Community	34.2%	34.6%
Disease Type		
NAFLD	18.6%	20.3%
Non-cirrhotic NASH	59.9%	57.2%
Cirrhotic NASH	21.5%	22.5%
Observed CV event within 1 year	3.5%	4.9%
Observed CV event within 3 years	7.1%	9.2%
Observed CV event within 5 years	11.3%	11.8%

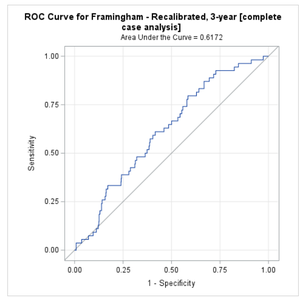
Note: The percentage of patients with an event within 1, 3, and 5 years is calculated among the subset of patients with at least 1, 3 or 5 years of follow-up data, respectively
[1]The Framingham and PCE risk equations were derived/validated using different populations (e.g. Framingham – aged 30-74; PCE – non-Hispanic white or black, age 40-79 with total cholesterol, HDL, and systolic blood pressure within certain ranges)

RESULTS

- In total, among adult participants enrolled in the US in TARGET-NASH, 980 patients in the Framingham and 587 patients in the PCE cohort had all necessary data for the calculation of CV risk
- 274 Framingham and 169 PCE cohort patients had at least five years of follow-up
- Framingham five-year predicted CV risk was significantly greater among patients who did vs. did not experience a CV event within 5 years (13.7% [SD=9.0] vs. 10.5% [SD=8.8]; p=0.02)
- There was no statistically significant difference in the PCE five-year predicted CV risk between patients who did vs. did not experience a CV event within 5 years
- The AUROC was 0.62 (95% CI 0.51, 0.73) for Framingham and 0.58 (95% CI 0.44, 0.72) for PCE at five years
- Worst predictive performance was among the subgroup of cirrhotic NASH patients for both risk equations
- Analyses of model calibration revealed a statistically significant lack of calibration for both tools at five years (Framingham: χ^2=25.58, p=0.001; PCE: χ^2=33.86, p<0.001)

Figure 1. Framingham ROC curves





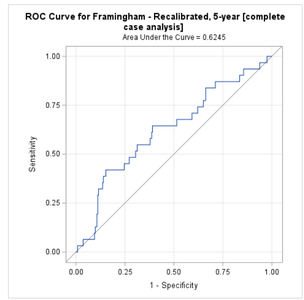
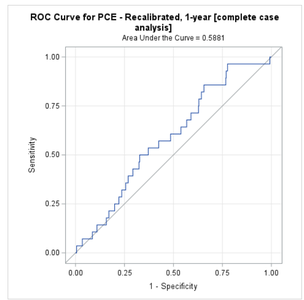
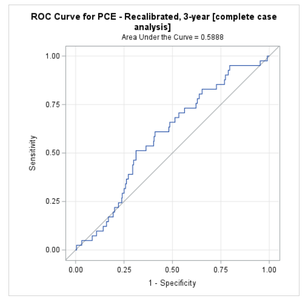


Figure 2. Pooled Cohort Equations ROC curves





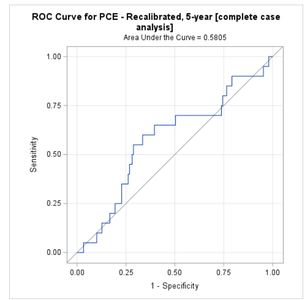


Table 2. Framingham Predictive Performance over 5 years

	1-year	3-year	5-year
AUROC (95% CI)	0.59 (0.51, 0.67)	0.62 (0.55, 0.69)	0.62 (0.51, 0.73)
NAFLD	0.58 (0.42, 0.73)	0.62 (0.48, 0.76)	0.65 (0.45, 0.84)
Non-cirrhotic NASH	0.70 (0.55, 0.85)	0.71 (0.62, 0.81)	0.74 (0.58, 0.89)
Cirrhotic NASH	0.44 (0.32, 0.56)	0.45 (0.33, 0.56)	0.40 (0.21, 0.60)

Table 3. Pooled Cohort Equations Predictive Performance over 5 years

	1-year	3-year	5-year
AUROC (95% CI)	0.59 (0.49, 0.69)	0.59 (0.51, 0.67)	0.58 (0.44, 0.72)
NAFLD	0.68 (0.48, 0.87)	0.64 (0.44, 0.85)	0.74 (0.42, 1.00)
Non-cirrhotic NASH	0.65 (0.45, 0.85)	0.64 (0.49, 0.78)	0.57 (0.30, 0.84)
Cirrhotic NASH	0.40 (0.25, 0.54)	0.42 (0.29, 0.55)	0.38 (0.19, 0.57)

CONCLUSIONS

- Framingham and PCE may have poor predictive accuracy for CVD risk in NAFLD/NASH cohorts, thus presenting a need for better risk equations to predict CV outcomes among patients with NAFLD and NASH as CVD is one of the top causes of death among this population
- Poor model calibration was most apparent among the upper decile of predicted risk, with predicted values far exceeding the observed
- Lack of ten-year follow up and unmeasured risk factors may explain some of the residual overestimation not accounted for in our models

LIMITATIONS

- The retrospective nature of this study limited the available data to 5 years of follow-up. Looking at the predictive performance of the Framingham and PCE over 10 years would potentially strengthen the predictive performance of the CV risk models

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