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RESEARCH ARTICLE

Assessment of Predictive Factors of Hepatic Steatosis Diagnosed by Vibration Controlled Transient Elastography (VCTE) in Chronic Hepatitis C Virus-Infected Patients

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Abstract

This retrospective, cross-sectional study aimed to evaluate the predictive factors of moderate/severe hepatic steatosis diagnosed by vibration-controlled transient elastography (VCTE). It included 158 adult patients with suspected non-alcoholic fatty liver disease (NAFLD) evaluated by VCTE in an outpatient setting of a community-based teaching hospital. Patients with significant alcohol consumption, oral contraceptive use, hepatitis B disease, autoimmune hepatitis, and primary biliary cirrhosis were excluded. Steatosis was categorized as S0−S1 (mild) and S2−S3 (moderate/severe) based on the controlled attenuation parameter (CAP) score. Results demonstrated the mean values of BMI ($p = 0.001$), kiloPascals [kPa] (fibrosis) raw score ($p = 0.009$), obesity ($p = 0.001$), diabetes mellitus [DM] ($p = 0.014$), and comorbidities status [chronic hepatitis C(HCV), DM, obesity, HCV+DM] ($p = 0.028$) were significantly different between the two arms of the study *viz.* S0−S1 (mild) and S2−S3 (moderate/severe). A multinomial logistic regression analysis of the comorbidities associated with hepatic steatosis revealed a good level of prediction (R^2-0.584) for hepatic steatosis. Of all the variables analyzed, obesity was the most impactful vavriable. Furthermore, the −2 log-likelihood of the regressed model in patients with HCV and hepatic steatosis did not show a significant correlation when adjusted for obesity. Obesity had a significant independent association with steatosis (chi-square value = 52, df = 12). Interestingly, DM independently predicted a weak association with steatosis (chi-square value = 0.825, df = 3). In conclusion, our study demonstrates that hepatic steatosis is independently associated with metabolic parameters like obesity and DM. Management of these risk factors in patients with HCV may be vital to reducing the risk of steatosis and progression to fibrosis.

Keywords: Hepatitis C virus (HCV), Steatosis, VCTE, CAP, Obesity, NAFLD

1. Introduction

Both hepatitis C virus (HCV) infection and non-alcoholic fatty liver disease (NAFLD) are significant causes of liver-related morbidity and mortality. HCV is a significant cause of chronic liver disease, with about 170 million people infected worldwide. The severity of the disease varies widely from asymptomatic chronic infection to cirrhosis and hepatocellular carcinoma (HCC).[1] Hepatic steatosis is defined as excessive fat accumulation in the liver (>5% involvement). It is currently the most common cause of chronic liver disease worldwide.[2,3]

In chronic HCV patients, the prevalence of steatosis ranges from 40% to 86% (mean, 55%).[4,5] Most patients (78%) have mild steatosis affecting less than

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30% of hepatocytes. Thus, steatosis occurs more frequently in patients with HCV (55%) than in the general population (20%–30%) of adults in the western world.[6] In non-diabetic, overweight patients, moderate or severe steatosis is present in only 10%–15% of genotypes 1 and 4 as compared with 40% of genotype 3 patients.[7,8]

Frequency of NASH ranged from 12.6% to 30.4% among obese patients. The rate of disease progression was associated with age, ethnicity, genetics, and presence of comorbidities (e.g obesity, T2DM, and hypertension).[9] Among 10 studies that estimated the prevalence of NASH, the global prevalence of NASH among individuals with T2DM was 37.3% (95% CI 24.7–50.0%). Seven studies estimated the prevalence of advanced fibrosis in patients with NAFLD and T2DM to be 17.0% (95% CI 7.2–34.8).[10]

Conventional ultrasonography (USG) is a non-invasive, cost-effective, rapid technique that detects patients with chronic liver diseases; however, it cannot quantify the degree of steatosis independently.[9,10] Vibration-controlled transient elastography (VCTE) is a novel, non-invasive method for fibrosis staging using liver stiffness measurement.[11] Furthermore, through the embedded controlled attenuation parameter (CAP) tool, VCTE can simultaneously assess liver steatosis by estimating the total ultrasonic attenuation.[12] Ultrasound elastography methods are becoming the standard of care as a non-invasive method to assess liver fibrosis and can be used as an alternative to invasive liver biopsy.[13] Furthermore, to the best of our literature survey, there have been a limited number of published reports available for predictive factors for the prevalence of steatosis in a large cohort of chronic HCV infected patients by using VCTE. Thus, the present study was conducted to assess the predictive factors of hepatic steatosis diagnosed by VCTE in chronic HCV infected patients.

2. Methods

This retrospective cross-sectional single-center study was conducted at a community hospital in central Massachusetts. A cohort of 158 adult patients evaluated by VCTE for suspected non-alcoholic fatty liver disease (NAFLD) was included. The institutional review board approved the study. Patients with significant alcohol consumption, drugs associated with hepatotoxicity, hepatitis B, autoimmune hepatitis, and primary biliary cirrhosis were excluded. Steatosis was categorized as S0–S1 (mild) and S2–S3 (moderate/severe) based on the controlled attenuation parameter (CAP) score.

The attributes collected were the controlled attenuation parameter (CAP) score on VCTE, kilopascals (k-Pa), gender, age, body mass index (BMI),

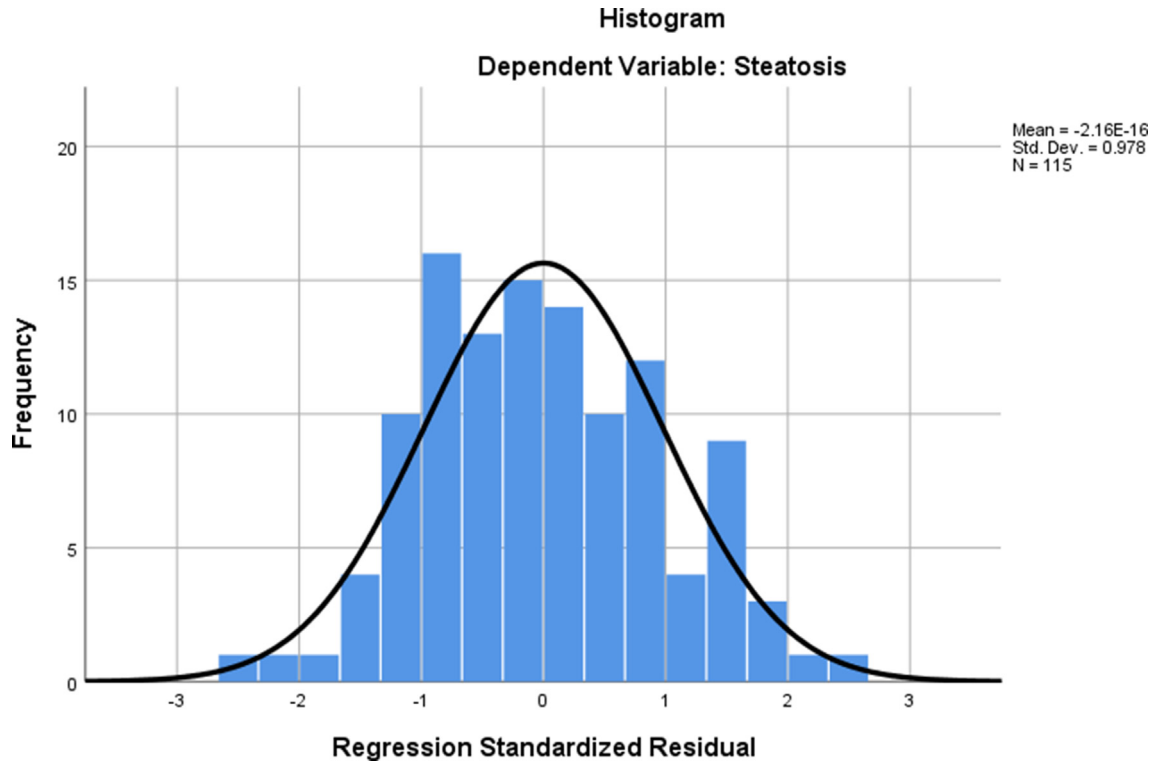

Fig. 1. Regression analysis of the risk factors associated with Hepatic Steatosis: Histogram.

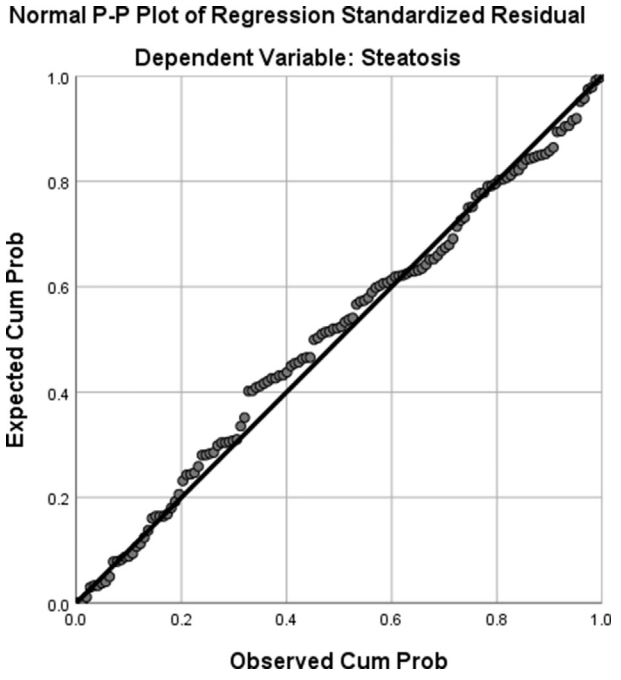

Fig. 2. Regression analysis of the risk factors associated with Hepatic Steatosis: P−P plot of regression standardized residual.

hypothyroidism, diabetes mellitus (DM) status, statin use, HCV status with genotype, transaminases, platelets, apolipoprotein, alpha-2 macroglobulin, hemoglobin A1c (HbA1C), triglycerides, lipid profile, and anti-hyperglycemic medications.

The results were tabulated and statistically analyzed using computer software (SPSS version 25 for Windows, SPSS Inc., Chicago, IL). Descriptive statistics included mean and standard deviation for quantitative variables and numbers with percentages for qualitative variables. Continuous variables were assessed using an unpaired t-test, and categorical variables using Chi-square with $p < 0.05$ were considered statistically significant. A multinominal logistic regression analysis was done to study the relationship between the CAP score (dependent variable) and significant covariates (independent variables). For this purpose, firstly, a null model was created to compute an intercept (the mean value of the dependent variable when all the independent variables are equal to zero) and a final model (where the dependent variable was calculated as a function of all the independent variables combined). Secondly, the null model was tested for goodness-of-fit by nesting it in the fitted model to ensure validity. For this, a pseudo-R- square was calculated by three different models. The model fitting criteria used was −2 log-likelihood (LL), tested by the above methodology. An LL-based pseudo-R- square was measured to compare the LL of the estimated model and the LL of the null model. There were five variables used in the regression analysis. Hepatic steatosis was the dependent variable, and HCV, DM, Obesity, and DM + HCV were the independent variables.

3. Results

Of the 158 patients analyzed, 22 met our exclusion criteria. Therefore, our study population consisted of 136 patients and was analyzed using their demographic information and CAP scores (see Figs. 1 and 2).

In comparison to CAP grade: S0−S1 (mild steatosis), patients with grade S2−S3 (moderate/severe steatosis) had a higher mean BMI: 32.46 as compared to 27.05 ($p = 0.001$), higher mean fibrosis raw score (k-Pa): 14.94 as compared to 8.82 ($p = 0.009$) (Table 1).

Table 1. Study subjects (continuous variables).

Characteristics	Steatosis (CAP grade)	N	Mean	Std. Dev	Mean Difference	p-value
AGE	S0 − S1	65	50.52	13.077	−3.040	0.171
	S2−S3	71	53.56	12.682		
BMI	S0 − S1	65	27.05	4.368	−5.419	**0.001***
	S2−S3	71	32.46	5.850		
KPA (fibrosis)	S0 − S1	65	8.82	12.096	−6.128	**0.009***
Raw Score	S2−S3	71	14.94	14.606		
Platelets	S0 − S1	63	25.73	16.872	−0.208	0.948
	S2−S3	65	25.94	19.358		
Apolipoprotein	S0 − S1	43	157.81	39.530	−87.944	0.263
	S2−S3	33	145.76	56.851		
a 2- macroglo	S0 − S1	42	29.24	9.894	−1.418	0.612
bulin	S2−S3	32	30.66	14.043		
Triglycerides	S0 − S1	46	35.74	27.928	7.628	0.125
	S2−S3	54	28.11	21.339		

$p < 0.05$.

Table 2. Study subjects (categorical variables).

Patient Characteristics	S0–S1 (mild)	S2–S3 (mod/severe)	Total	Chi-square	p-value
	Obesity				
Normal	20	5	25	36.369	**0.0001***
BMI:18.5–24.9 kg/m^2	30.8%	7.0%	18.4%		
Overweight	33	17	50		
25–29.9	50.8%	23.9%	36.8%		
Obesity	12	49	61		
>30	18.5%	69.0%	44.9%		
	Diabetic status			6.088	**0.014***
Diabetes Mellitus (DM)	13	28	41		
	20.0%	39.4%	30.1%		
Non-DM	52	43	95		
	80.0%	60.6%	69.9%		
	HIV			0.006	0.938
Negative	64	69	133		
	98.5%	97.2%	97.8%		
Positive	1	2	3		
	1.5%	2.8%	2.2%		
	Comorbidities			9.080	**0.028***
Hepatitis C	44	30	74		
	67.7%	42.3%	54.4%		
Hepatitis C + DM	7	15	22		
	10.8%	21.1%	16.2%		
DM	6	13	19		
	9.2%	18.3%	14.0%		
No Hepatitis C or diabetes	8	13	21		
	12.3%	18.3%	15.4%		

$p < 0.05$.

Obesity (p-0.0001*), DM (p-0.014*), and active comorbidities such as HCV, concomitant HCV with DM (p-0.028*) were significantly different between study groups viz. S0–S1 (mild) and S2–S3 (moderate/severe) (Table 2). Row statistic for comorbidities in Table 2 further showed that 40% of patients with only hepatitis C, 68% of hepatitis C patients with DM, 68% with DM and, 61% non-hepatitis C, non-DM patients (p-0.028*) had moderate to severe hepatic steatosis.

Table 3. HCV genotype and steatosis (% calculated against entire sample size).

HCV Genotype	S0–S1	S2–S3
1	29 (36.7%)	24 (30.3%)
2	1 (0.012%)	3 (0.03%)
3	9 (0.11%)	6 (0.07%)
4	3 (0.03%)	2 (0.02%)
6	1 (0.012%)	1 (0.012%)

Chi square - 1.6645.
p value - 0.79.

On the assessment of steatosis based on the genotype of HCV, we found that most patients with steatosis were in patients with HCV genotype 1 (Table 3). The distribution of severity of mild and moderate/severe steatosis was similar for each genotype ($p = 0.79$).

A null model (Table 4) showed a strong relationship between comorbidities and the dependent variable: steatosis. The degrees of freedom (df) were 24 ($p = 0.0001$). For the goodness of fit testing, multiple pseudo-R^2 values (Table 5) were compared for the same predicted outcome (CAP score), namely, Cox and Snell value- 0.479, Negelkerke value of 0.520, and McFadden 0.257. The highest value in the Negelkerke model predicted that all independent variables combined caused a 52% change in the dependent variable.

The standard beta coefficient results of the risk factors associated with hepatic steatosis in multiple regression analysis depicted that obesity class had a

Table 4. Model summary analysis of the risk factors associated with Hepatic Steatosis.

Model Summary				
Model	Model fitting criteria:	Likelihood Ratio tests		
	−2 log-likelihood	Chi-square	df	sig.
Final model	113.377	74.882	24	0.0001

a. Predictors: (Constant), Hepatitis C +DM, Obesity Class, DM, and Hepatitis C.

Table 5. Showing various models tested for goodness of fit.

Pseudo-R^2	
Cox and Snell	0.479
Nagelkerke	0.520
McFadden	0.257

statistically significant relationship with steatosis among all other variables. Furthermore, it showed that each obesity class increase was associated with steatosis by 50.8 units, as depicted in Table 6.

The findings described in Table 7 showed that the −2 LL in patients with only HCV and HCV with DM revealed that omitting the effect of obesity resulted in zero degrees of freedom (df 0). It appeared that the initial association of patients with HCV and HCV + DM and moderate/severe hepatic steatosis was confounded by underlying obesity in the patients. Once the variable was controlled for, the association ceased to exist. Obesity independently had a significant association with hepatic steatosis (chi-square value 52, df 12). Interestingly, DM independently predicted a weak association with steatosis (chi-square value 0.825, df 3).

4. Discussion

Chronic infection with HCV is one of the leading causes of cirrhosis and hepatocellular carcinoma. Surveillance of HCV patients is an essential strategy to prevent liver-related mortality, including the pre/post-antiviral treatment states. Ultrasound elastography techniques are emerging as crucial methods in assessing liver diseases, given their rapid, non-invasive, and cost-effective characteristics. VCTE measures liver stiffness, and the ultrasonic attenuation through the embedded CAP provides the clinician a tool for assessing fibrosis, cirrhosis, and steatosis in a non-invasive manner. Moreover, standardized liver stiffness values enable the proper staging of underlying fibrosis, facilitating accurate identification of patients at high risk for complications and early intervention to prevent progression. In addition, VCTE is a valuable technique in evaluating liver fibrosis before HCV therapy. VCTE is currently not readily available at all centers despite gaining worldwide popularity.

The present study comprises a cohort of 136 adult patients with suspected NAFLD. It evaluated the relationship of various clinical factors associated with moderate/severe liver steatosis identified by the novel CAP score. In our study, we found the mean values of BMI (p-0.001), k-Pa (fibrosis) raw score (p-0.009) to be significantly different between study groups *viz.* S0−S1 (mild) and S2−S3 (moderate/severe).

The BMI, diabetes, and hepatitis C status of the cohort enrolled in our study differed significantly between study groups; S0−S1 (mild) and S2−S3 (moderate/severe). Identification of factors related to liver steatosis before treatment might help select patients that could need a careful follow-up even after sustained virological response to monitoring liver fibrosis progression due to additional

Table 6. Standard Beta coefficient results of the risk factors associated with Hepatic Steatosis.

Model	Unstandardized Coefficients		Standardized Coefficients	T	Sig.
	Beta	Std. Error	Beta		
Hepatitis C	−11.357	17.076	-0.070	-0.665	0.507
Obesity	37.152	5.44	0.508	6.823	0.0001
DM	9.088	7.09	0.116	1.281	0.203
Hepatitis C+DM	10.729	10.2	0.097	1.042	0.299

a. Dependent Variable: Steatosis.

Table 7. Results of likelihood ratio tests of the risk factors associated with hepatic steatosis on multivariate regression analysis.

Effect	Model Fitting Criteria	Likelihood Ratio Tests		
	−2 Log Likelihood of Reduced Model	Chi-Square	df	Sig.
Intercept	113.377[a]	0.000	0	.
Gender	118.582	5.206	3	0.157
Obesity Class	165.619	52.242	12	0.000
Hepatitis C	113.377[a]	0.000	0	.
DM	114.202	0.825	3	0.843
Hepatitis C + DM	113.377[a]	0.000	0	.

The chi-square statistic is the difference in −2 log-likelihoods between the final and reduced models. The reduced model is formed by omitting an effect from the final model. The null hypothesis is that all effect parameters are 0.

[a] This reduced model is equivalent to the final model because omitting the effect does not increase the degrees of freedom.

metabolic factors and other extrahepatic complications such as cardiovascular outcomes. Currently, most guidelines suggest that patients with advanced fibrosis should periodically be monitored in the outpatient clinic even after sustained virological response.[15,16] However, those who present only with moderate/severe steatosis and the related factors identified in this study, even with no fibrosis, may still be required to follow up regularly until clear evidence is available regarding metabolic factors and the related outcomes in patients who achieved sustained virological response. Recently Serfaty et al. suggested an algorithm where patients who still had metabolic factors such as high BMI or DM should be followed annually with non-invasive markers of fibrosis.[17]

In our study, the log-likelihood ratio measured the regression of each selected independent variable individually, adjusting for the interplay of obesity in hepatitis C patients and omitting effects of the same on the outcome (hepatic steatosis). Here, we interestingly found that the chi-square statistic was 0 for patients with hepatitis C when adjusted for confounding, indicating that active infection did not play a role in hepatic steatogenesis directly.

Findings like our study have been previously reported. Motamed et al., in their analysis of 5052 subjects, found a significant positive correlation between serum fatty liver index (FLI) and NAFLD (AUC = 0.8656, 95% CI 0.8548–0.8764); the findings were confirmed by binary regression. FLI was highly associated with NAFLD, to the point that even a one-unit increase in FLI increased the chance of NAFLD occurrence by 5.8% and showed good predictive performance in the diagnosis of NAFLD.[18] Additionally, this is similar to Dehnavi et al., who analyzed 212 patients with NAFLD and found that FLI was significantly associated with NAFLD (OR = 1.062, 95%CI 1.042–1.082, $p < 0.001$), and that mean FLI, BMI, WC, TG, and GGT were all significantly higher in NAFLD patients as compared to non-NAFLD participants, and that a one-unit increase in FLI elevated the chance of developing NAFLD by 6.2%.[19]

Although this study was not designed to hypothesize about the pathophysiological pathways of steatosis in HCV patients, it is possible to speculate that there may be a synergy between the already known effect of HCV on metabolic pathways in patients with a higher BMI, leading to a higher prevalence of steatosis in this group. Thomopoulos et al. reported that steatosis in HCV patients is higher than in HBV patients, maybe due to the HCV viral impact on metabolic pathways leading to insulin resistance and metabolic syndrome, usually absent in HBV patients.[14] Thereby, we could hypothesize that VCTE should be used for non-hepatitis C patients with long-standing type 2 diabetics or obese patients with multiple comorbidities to screen for steatosis. We need further studies to recommend whether VCTE could be included in the regular DM screening like an eye exam, foot exam, and BP/Lipid profile management. A screening test that primary care physicians can order.

A possible question for future prospective studies is if a patient has achieved sustained viral response (SVR) with directly-acting-antiviral (DAA) treatment, should they still be monitored with serial VCTE if they have certain risk factors like obesity and DM to prevent progression of steatosis to cirrhosis.

Other studies have reported similar findings. Siddiqui et al. performed a prospective study of 393 adults with NAFLD who underwent VCTE within one year of liver histology and found that the CAP value is positively associated with the severity of hepatic steatosis. The cross-validated AUROC is 76% for classifying patients with ≥5% steatosis on histology.[20] Eddowes et al. evaluated 450 patients and assessed the diagnostic accuracy of CAP and liver stiffness measurement against liver biopsy and found that CAP by TE is an accurate non-invasive method for assessing liver steatosis in patients with NAFLD with an AUROC of 0.87 (95% CI 0.82–0.92), the sensitivity of 0.80, and specificity of 0.83.[21]

Although liver biopsy is the gold standard to detect fibrosis and liver steatosis, it cannot be used as a screening tool and follow-up of patients with chronic liver disease due to its invasive nature. Notwithstanding, other non-invasive methods have been developed to diagnose steatosis and quantify fat.[22–25] Among image devices, ultrasonography is the most frequently used method for liver imaging, and steatosis can be assessed by comparing parenchymal echogenicity with kidney echogenicity.[26] The CAP score can be widely applied to both diagnose and quantify liver steatosis in HCV-infected patients helping to identify those that might need further follow-up regarding metabolic optimization to help preclude liver disease progression.[27–30]

4.1. Limitations of the study

The predominant genotype (GT) of our study was GT 1, which has been described previously to predispose metabolic syndrome. We did not sub-

stratify for genotype during the regression analysis in our analysis. We hence cannot comment on which genotype independently attributed to hepatic steatosis when controlled for obesity.

We have not presented data on the results of the CAP score after these patients achieved SVR with DAA. It would be intriguing to see an improvement in the steatosis severity after treatment.

4.2. Strengths of the study

Our dataset predominantly existed of patients with HCV. However, despite a smaller sample size of non-HCV patients, we could still detect a statistical difference and further reproduce it on regression analysis.

5. Conclusion

Our study demonstrates that hepatic steatosis is independently associated with metabolic parameters like obesity and DM. The most significant risk factor for steatosis in untreated hepatitis C patients is their BMI. The management of obesity in patients with HCV may be necessary to reduce the risk of steatosis progression and improve their steatosis score.

Disclaimer

The following article is currently not submitted elsewhere for review.

The abstract portion has been presented at MA-ACP chapter on 10/21 in the poster competition and received an honorary mention award.

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Conflict of interest

All authors declare no conflict of interest.

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