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ARTICLE

Leukocyte cell-derived chemotaxin 2 correlates with pediatric non-alcoholic fatty liver disease

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Abstract

Non-alcoholic fatty liver disease (NAFLD), newly renamed metabolic dysfunction-associated liver disease (MASLD), is a leading cause of liver disease in children and adults. There is a paucity of data surrounding potential biomarkers and therapeutic targets, especially in pediatric NAFLD. Leukocyte cell-derived chemotaxin 2 (LECT2) is a chemokine associated with both liver disease and skeletal muscle insulin resistance. Our aim was to determine associations between LECT2 and common clinical findings of NAFLD in pediatric patients. Enzyme-linked immunosorbent assay (ELISA) was used to measure serum LECT2 concentrations in children (aged 2–17 years) with and without NAFLD. LECT2 concentrations were then correlated to clinical parameters in NAFLD. Mean LECT2 was significantly elevated in children with NAFLD versus healthy controls ($n = 63$ vs. 42, 5.83 ± 1.98 vs. 4.02 ± 2.02 ng/mL, $p < 0.005$). Additionally, LECT2 had strong correlations with body mass index (BMI) (Pearson $r = 0.301$, $p = 0.002$). A LECT2 concentration of 3.76 mg/mL predicts NAFLD with a sensitivity of 90.5% and specificity of 54.8%. Principal component analysis and logistic regression models further confirmed associations between LECT2 and NAFLD status. This study demonstrates increased serum LECT2 concentrations in pediatric NAFLD, which correlates with BMI and shows strong predictive value within these patients. Our data indicate that LECT2 is a potential diagnostic biomarker of disease and should be further investigated in pediatric as well as adult NAFLD.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Pediatric non-alcoholic fatty liver disease (NAFLD) has an increasing disease burden in the United States with limited treatment options and biomarkers of disease. Leukocyte cell-derived chemotaxin 2 (LECT2) is a known biomarker and potential therapeutic target in adult NAFLD.

WHAT QUESTION DID THIS STUDY ADDRESS?

We sought to determine how LECT2 serum levels in pediatric NAFLD compared to healthy controls. Our secondary aim was to assess correlations between LECT2 and other common markers of NAFLD and liver disease.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

LECT2 is a potential biomarker of disease in pediatric NAFLD and correlates with pediatric body mass index. How might this change clinical pharmacology or translational science? Elevated levels of LECT2 have potential diagnostic capability and should be further investigated.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD), newly renamed metabolic dysfunction-associated liver disease (MASLD), is one of the most important diseases in the hepatology field and its incidence is increasing in adults as well as children.[1] Between 2009 and 2018, the incidence of diagnosed NAFLD increased from 36.0 per 100,000 to 58.2 per 100,000 children in a study by Sahota et al.[2] NAFLD itself represents a spectrum of disease. It includes simple histologic steatosis and proceeds to non-alcoholic steatohepatitis, progressive fibrosis, and eventual cirrhosis.[3] It is the second leading cause of liver transplantation in adults with many predicting that it will become the most common etiology.[4] Obesity, which has reached epidemic proportions in the United States with as many as 35.1% of US children classified as overweight or obese, is a major cause of NALFD and associated metabolic syndrome.[5] Beyond the connections with obesity, the mechanisms of NAFLD pathogenesis remain under investigation as it is a complex interplay between genetics, nutrition, physical activity, external exposures, the microbiome, and other undiscovered connections.[6] Pharmacologic treatments for NAFLD remain elusive and the bedrock of therapy remains lifestyle interventions such as increased physical activity and dietary changes.[7] Bariatric surgery is increasingly utilized but often reserved for more advanced cases of obesity.[8]

Despite the prevalence of NAFLD, gaps in knowledge persist. This is especially pertinent in pediatrics, where NAFLD is the most common liver disease of childhood and may be a cause of cryptogenic cirrhosis in adults.[9,10] Pediatric NAFLD and subsequent non-alcoholic steatohepatitis are both associated with lifelong risks of overall, cancer-, liver-, and cardiometabolic-specific mortality when compared to matched population controls in a study in Swedish children by Simon et al.[11] There is a paucity of data in pediatric patients on non-invasive biomarkers as well as potential therapeutic targets that either reduce steatosis or prevent NAFLD's fibroinflammatory process.[12,13]

Leukocyte cell-derived chemotaxin 2 (LECT2) is a chemokine, first discovered in 1996 as a chemotactic agent for neutrophils.[14] Recent studies show that LECT2 is utilized in multiple organ systems with implications for liver disease, insulin resistance, bone health, cancer signaling, among others.[14,15] Despite its strong associations with NAFLD and insulin resistance in adults, its association with NAFLD progression in pediatric patients has never been investigated.[15] We sought to determine LECT2 serum levels in pediatric NAFLD patients compared to healthy controls. Our secondary aim was to assess correlations between LECT2 and other markers of NAFLD such as body mass index (BMI), aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, random glucose level, and glycated hemoglobin (HbA1c). We found that children with NAFLD had elevated LECT2 concentrations compared to healthy controls. LECT2 correlates with BMI and an elevated concentration of LECT2 is predictive of NAFLD.

METHODS

Subject enrollment

Subjects were identified from May 2016 to April 2021. Pediatric subjects (aged 3–17 years) were recruited from the Division of Gastroenterology, Hepatology, and Nutrition at Children's Mercy – Kansas City. The NAFLD group was defined as those with imaging or histology consistent with hepatic steatosis and a clinical diagnosis of NAFLD by a hepatologist. Healthy controls were defined as those without history of liver disease or imaging/histology consistent with hepatic steatosis. Patients from both groups were excluded if they had diagnoses other than NAFLD that could predispose to steatosis and liver disease (such as inborn errors of metabolism) or alter results of liver functions tests (such as muscular dystrophies). A total of 63 pediatric subjects with NAFLD were enrolled in our study with 42 pediatric control subjects. All study activities were reviewed by the Institutional Review Board at Children's

Mercy – Kansas City and confirmed ethical approval to the guidelines of the 1975 Declaration of Helsinki.

Clinical data collection

Available clinical data including anthropometric measurements, laboratory results, radiographic data, and histology data were collected from the subject's electronic medical record at each institution by study personnel. Data were collected from the subject's most recent clinical visit.

Quantification of serum LECT2

Serum LECT2 concentrations were quantified using commercially available human LECT2 enzyme-linked immunosorbent assay (ELISA) kits (human leukocyte cell-derived chemotaxin 2 [LECT2] ELISA Kit,

TABLE 1 Patient characteristics.

Characteristic	Pediatric controls ($n=42$)	Pediatric NAFLD patients ($n=63$)	*P*-value
Female	32	15	<0.005
Male	10	48	<0.005
Mean age (years)	11.85714286	12.85714286	0.149
SD age (years)	3.886006343	3.135937082	–
Race/ethnicity	–	–	<0.005
Caucasian	38	25	–
Hispanic	1	32	–
African American	1	1	–
Asian	1	0	–
Multiracial	1	4	–
Unknown	0	1	–
Mean BMI	19.77756098	34.2	<0.005
SD BMI	4.49318583	7.058559993	–
Mean BMI *z*-score	0.19	2.411111111	<0.005
SD BMI *z*-score	1.10298514	0.430277896	–
Mean AST	29.57142857	61.88888889	<0.005
SD AST	8.631035484	40.07618193	–
Mean ALT	25.42857143	117.015873	<0.005
SD ALT	7.755856504	74.56075506	–
Mean TB	0.8	0.522222222	<0.005
SD TB	0.38539691	0.248508093	–
Mean random insulin level	6.635135135	85.72857143	<0.005
SD random insulin level	3.248094845	80.49497966	–
Mean random glucose level	81.78571429	97.14285714	<0.005
SD random glucose level	7.383355422	26.31806515	–
Mean HbA1c	5.2	5.5	<0.005
SD HbA1c	0.259052145	0.593232874	–
Mean LECT2	4.015360974	5.834325325	<0.005
SD LECT2	2.022934659	1.984936953	–
Mean female LECT2	3.93007043	5.36559809	0.03
SD female LECT2	1.988093932	2.161033084	–
Mean male LECT2	4.28829072	5.98080258	0.017
SD male LECT2	2.218035125	1.927251872	–

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; HbA1c, glycated hemoglobin; LECT2, leukocyte cell-derived chemotaxin 2; NAFLD, non-alcoholic fatty liver disease; SD, standard deviation; TB, total bilirubin.

Cat#EKU05623; Biomatik; Cambridge, Ontario, Canada). Samples were processed in duplicate according to the manufacturer's instructions.

Statistical analysis

All statistical analyses were performed using SPSS version 24.0.0.2 (International Business Machines Corp., Armonk, NY, USA). Subject characteristics were compared between groups using the independent samples *t*-test for continuous variables and the chi-square test for independence for categorical variables. Correlations between continuous variables were further analyzed by scatterplot analysis and Pearson correlation analysis. Receiver operating characteristic (ROC) curves were utilized to assess the ability of LECT2 to identify NAFLD.

Multivariate dimensionality reduction and modeling

The parameters subjected to analysis included AST, LECT2, gender, and race and ethnicity. Notably, ALT and BMI were deliberately excluded from consideration within the analysis due to pronounced correlations, as assessed by the two-tailed Pearson correlation, with ALT and LECT2, correspondingly.

The processes of principal component analysis (PCA) and logistic regression were conducted within the R studio environment, specifically utilizing R version 4.0.3. In the context of PCA, the variables were scaled, and the resultant eigenvectors were visually presented utilizing ggplot2 (version 3.3.3).

Manuscript development

All authors had access to the study data and have reviewed and approved the final manuscript.

RESULTS

Subject characteristics

Clinical data on study participants are included in Table 1. Predictable changes in clinical parameters such as body mass index (BMI), transaminase elevation, HbA1c, and random glucose were noted based on the presence or absence of NAFLD. Histology reports were available for six subjects with NAFLD. Median NAFLD activity score was 4/8 (range 3–5/8). Median fibrosis grade was 2/4 (range 0–2/4). Median percent steatosis was 20% (range 10%–40%). Subject-level data on histology can be found in Table S1.

Increased LECT2 levels in pediatric NAFLD

Mean LECT2 levels were higher in pediatric patients with NAFLD compared with controls with 5.83 ± 1.98 versus 4.02 ± 2.02 ng/mL, $p < 0.005$ (Table 1, Figure 1a). This difference persisted with statistical significance when groups were broken down by sex (Figure 1b).

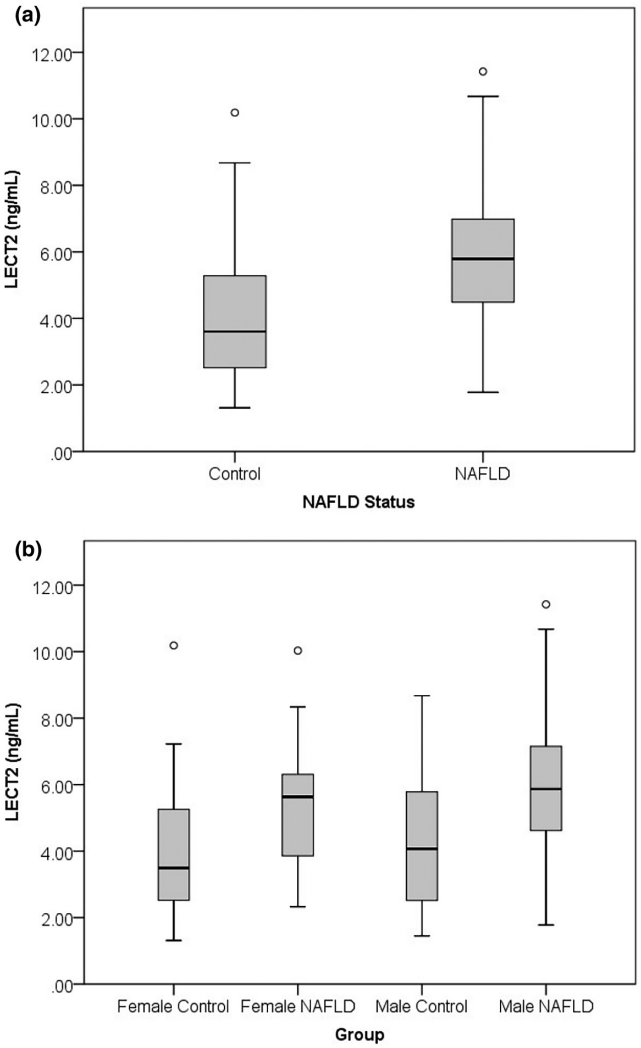


FIGURE 1 Serum leukocyte cell-derived chemotaxin 2 (LECT2) levels in pediatric non-alcoholic fatty liver disease (NAFLD) patients and controls. (a) Boxplot comparison of LECT2 concentration (ng/mL) in pediatric controls and those with NAFLD. Difference in means between controls and NAFLD, $p < 0.005$. The horizontal line denotes median value; box extends from the 25th to the 75th percentile of the distribution; vertical lines denote smallest and largest values; and dots denote outliers. (b) Boxplot comparison of LECT2 concentration (ng/mL) in pediatric controls and those with NAFLD group by sex. Difference in means between controls and NAFLD in females, $p = 0.03$, and males, $p = 0.017$. The horizontal line denotes median value; box extends from the 25th to the 75th percentile of the distribution; vertical lines denote smallest and largest values; and dots denote outliers.

Correlation of LECT2 with common clinical markers of disease in NAFLD

Scatterplots demonstrated positive and significant correlations between LECT2 and BMI ($R^2 = 0.090$, $r = 0.301$, $p = 0.002$) and BMI z-score ($R^2 = 0.169$, $r = 0.412$, $p < 0.005$; Figure 2). Scatterplots also demonstrated positive correlations with transaminases such as aspartate aminotransferase ($R^2 = 0.009$, $r = 0.093$, $p = 0.345$); however, only alanine aminotransferase approached predefined statistical significance ($R^2 = 0.031$, $r = 0.177$, $p = 0.071$; Figure 2). Remaining common clinical tests for insulin resistance and NAFLD did not reveal strong correlations with LECT2 including total bilirubin, random glucose level, and HbA1c (Figure S1). Table S1 includes details of individual histology reports and LECT2 levels.

Specificity and sensitivity of LECT2 as a biomarker

A receiver operating characteristic (ROC) curve demonstrated that LECT2 confirmed NAFLD with an acceptable area under the curve (Figure 3) with full specificity and sensitivity values as a supplemental figure (Table S2). A LECT2 concentration of 3.76 ng/mL diagnosed NAFLD with a sensitivity of 90.5% and specificity of 54.8%.

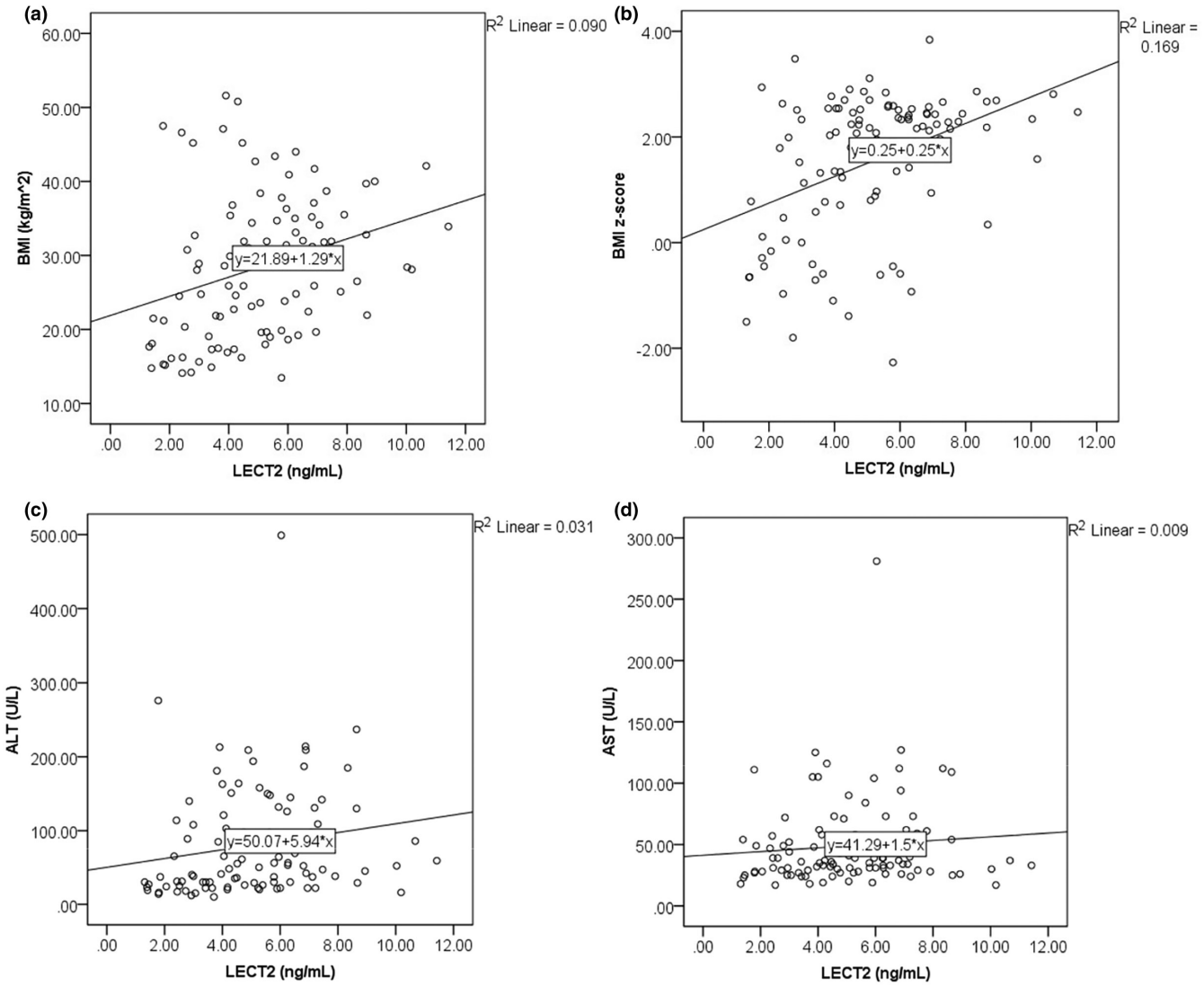
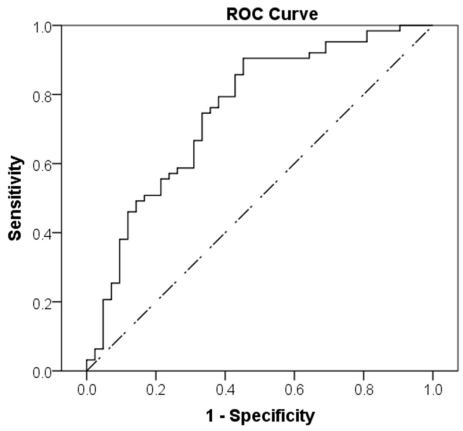


FIGURE 2 Serum leukocyte cell-derived chemotaxin 2 (LECT2) levels and their correlations with body mass index (BMI) and common markers of liver disease. (a) Scatterplot of pediatric LECT2 concentration (ng/mL) to BMI (kg/m^2) ($n = 105$, Pearson $r = 0.301$, $p = 0.002$). (b) Scatterplot of pediatric LECT2 concentration (ng/mL) to BMI z-score ($n = 105$, Pearson $r = 0.412$, $p < 0.005$). (c) Scatterplot of pediatric LECT2 concentration (ng/mL) to alanine aminotransferase (ALT) (U/L) ($n = 105$, Pearson $r = 0.177$, $p = 0.071$). (d) Scatterplot of pediatric LECT2 concentration (ng/mL) to aspartate aminotransferase (AST) (U/L) ($n = 105$, Pearson $r = 0.093$, $p = 0.345$).



Area Under the Curve

Test Result Variable(s): Pediatric LECT2

Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
0.752	0.050	0.000	0.655	0.850

a. Under the nonparametric assumption

b. Null hypothesis: true area = 0.5

FIGURE 3 Receiver operating characteristic (ROC) curve of leukocyte cell-derived chemotaxin 2 (LECT2) to predict non-alcoholic fatty liver disease (NAFLD) ($n = 105$, $p < 0.005$).

Multivariate dimensionality reduction and modeling

PCA was conducted on the variables ALT, LECT2, gender, and race and ethnicity to succinctly portray and graphically represent the complex multivariate dataset (refer to Figure 4). The first principal component (PC1) accounted for 40.18% of the total variance, while the second principal component (PC2) explained 23.97% of the variance within the data. Notably, a distinct demarcation between the NALD and control groups emerged as a consequence of the interplay between PC1 and PC2. PC1 exhibited a more pronounced contribution to this observed separation. BMI was not included in the PCA statistical analysis; however, BMI was overlayed to visualize the individual that had high BMI had high LECT2.

To ascertain the variables substantially influencing the variability of NAFLD status, a logistic regression model was leveraged. Given the evident correlation between ALT and AST ($r^2 = 0.92$, p-value <2.2e-16), as well as between LECT2 and BMI ($r^2 = 0.30$, p-value = 0.0019), the analysis excluded ALT and BMI. Table 2 encapsulates the model's concise representation, delineating the statistical summaries of all variables that significantly contributed to explicating NAFLD status. As foreseen, both LECT2 and ALT demonstrated statistically significant associations with NAFLD status. Intriguingly, gender and race also exhibited the capacity to elucidate NAFLD status. This phenomenon could potentially be attributed to the disproportionate representation of males within the NAFLD cohort, coupled with variations in racial distribution across the comparative groups (Figure 5).

DISCUSSION

As the most common liver disease in children, pediatric NAFLD is a costly public health burden with significant morbidity and mortality.[4,16] Manifesting earlier in life, pediatric patients have several years beyond their adult counterparts to develop complications from chronic inflammation, fibrosis, and end-stage liver disease. The early development of this fibroinflammatory milieu is a suspected cause of cryptogenic cirrhosis, the increasing incidence of non-B hepatitis and non-C hepatitis hepatocellular carcinoma, and lifelong increased risks of overall, cancer-, liver-, and cardiometabolic-specific mortality.[11,17,18] Unfortunately, routine biochemical testing is non-specific for NAFLD and does not clearly correlate with disease progression.[19–21] While liver biopsy remains the gold standard for diagnosis and assessment of fibrosis, it can be costly, invasive, and carries some risk while not always providing an accurate diagnosis, such as the setting of cryptogenic cirrhosis.[17] The development of accurate non-invasive biomarkers has the potential to streamline care and improve diagnosis and outcomes.

Our study is the first to assess LECT2 levels in the setting of NAFLD with a pediatric patient population. This is important as diseases do not always present with the same mechanisms between pediatric and adult patients. Our study reveals positive correlations between LECT2 and BMI/BMI z-score with statistical significance. Mean LECT2 is clearly increased in the setting of NAFLD, and ROC demonstrates an acceptable ability to screen for NAFLD non-invasively. This was further supported by logistic regression models and our multivariate PCA analysis which confirmed associations between LECT2 and NAFLD status. Further study will be critical in the development of non-invasive testing that could avoid the cost and relative risk of procedures such as liver biopsy, and this study is intended as a first step in this process. Additional research is needed to determine precise diagnostic values for LECT2 by age and its associations with disease progression.

Our study is not without limitations. With smaller subject numbers, this study is intended as pilot data to guide future research. Future studies with more subjects and improved baseline matching would strengthen this relationship. While transaminases and BMI are commonly used as clinical surrogates of steatohepatitis, it is known that they do not always directly correlate with histologic disease.[20] Liver histology was not available in high enough

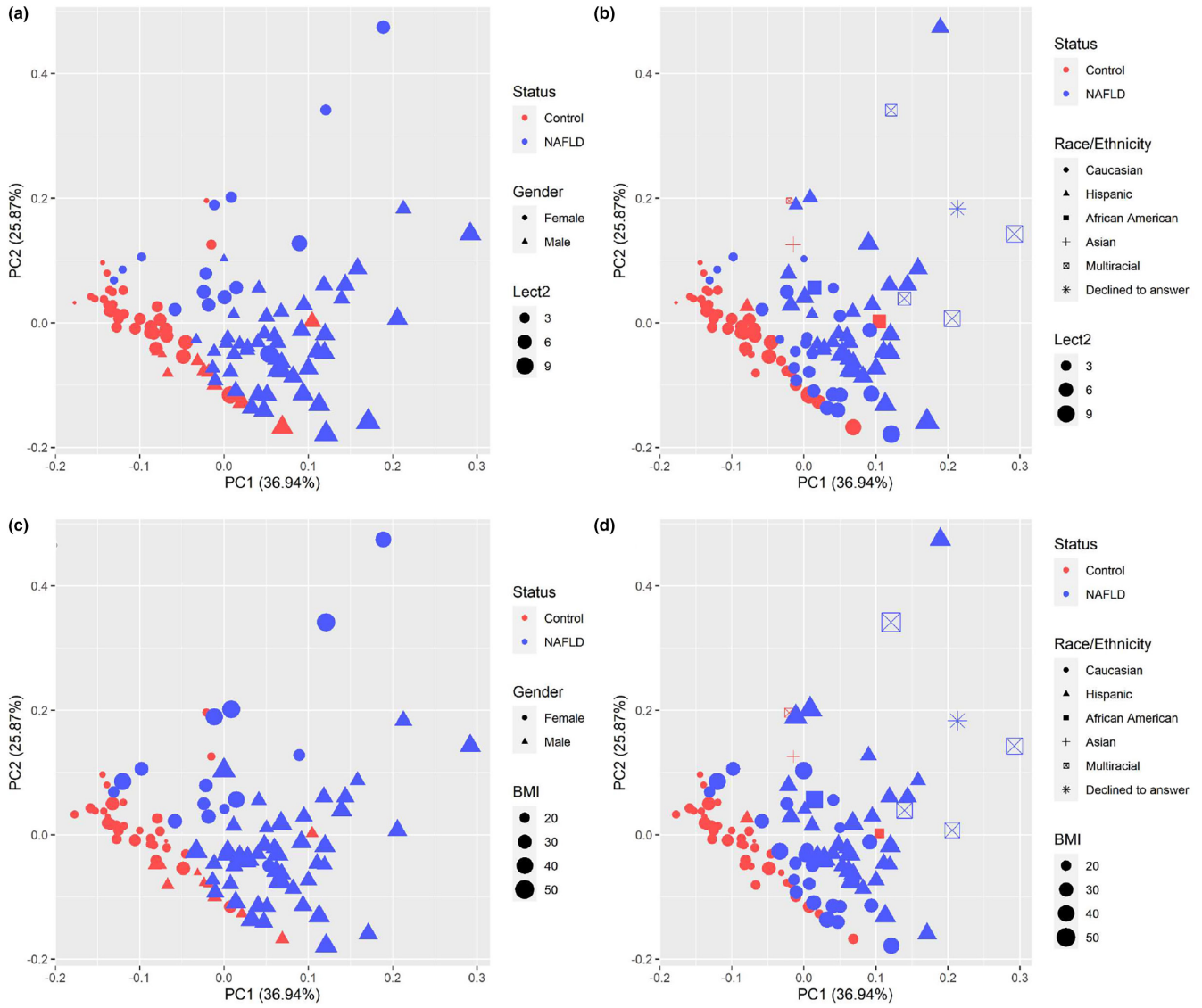


FIGURE 4 Principal component analysis (PCA) of the variables alanine aminotransferase (ALT), leukocyte cell-derived chemotaxin 2 (LECT2), gender, and race/ethnicity. PCA plots showing (a) gender, non-alcoholic fatty liver disease (NAFLD) status, and LECT2 levels; (b) race/ethnicity, NAFLD status, and LECT2 levels; (c) gender, NAFLD status, and body mass index (BMI); and (d) race/ethnicity, NAFLD status, and BMI.

TABLE 2 Summary table of logistic regression model showing beta estimate together with beta 95% confidence interval, standard error, and significant test using the *z* statistic for each variable.

Parameter	Estimate	95% Interval	SE	*Z* value	Pr(>|z|)
(Intercept)	−14.37707	±8.731	3.57469	−4.022	5.77E-05
LECT2	0.74597	±0.422	0.24973	2.987	0.002817
Gender	2.99826	±1.636	0.93044	3.222	0.001271
Race	1.2567	±0.936	0.53076	2.368	0.017899
ALT	0.23922	±0.104	0.06507	3.676	0.000236

Abbreviations: ALT, alanine aminotransferase; LECT2, leukocyte cell-derived chemotaxin 2; SE, standard error.

numbers for statistical analysis of NAFLD activity score, fibrosis grade, percent steatosis, or type 1 versus 2 non-alcoholic steatohepatitis as the clinical role of liver biopsy is not well established and relatively controversial in most routine cases of pediatric NAFLD.[22,23] There may also be differences between patients who have simple steatosis, non-alcoholic steatohepatitis, and progressive fibrosis that are beyond the scope of our study. Non-invasive markers of fibrosis such as FibroScan® were not available in our clinical practice at the time of sample collection making

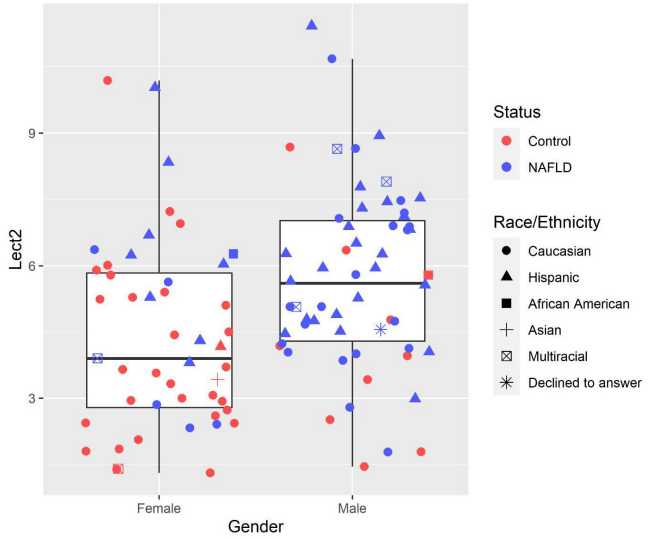


FIGURE 5 Box and whisker plot depicting leukocyte cell-derived chemotaxin 2 (LECT2) levels, stratified by gender. Each datapoint denotes an individual patient, with point shape indicating race/ethnicity and color denoting disease status.

correlations with fibrosis difficult. Additionally, LECT2 may have an improved ability to detect NAFLD and quantify severity as part of a diagnostic panel as opposed to solitary testing.

Studies have shown changes in serum or plasma concentration of LECT2 in coronary artery disease, amyloidosis, liver fibrosis, and NAFLD among others.[24–27] Data continue to emerge that LECT2 is a bridge connecting insulin resistance with NAFLD.[28] It has a baseline role in both liver homeostasis as well as hepatic inflammation independent of metabolic syndrome.[15] LECT2 knockout mice have increased inflammatory cell presence on liver histology compared to control groups showing its essential role in homeostasis outside of the setting of disease.[29] These mice also have higher peaks of transaminase elevation and increased degenerative changes on histology after concanavalin A administration.[29] LECT2 is also directly regulated by the Wnt/β-catenin pathway, an essential signaling pathway for liver regeneration.[30,31] In previous research, our group demonstrated that changes in serum LECT2 levels in adult patients with acute liver failure was associated with higher survival.[32] Together, these studies suggest the importance of LECT2 in cases of liver disease.

In the field of insulin resistance, Lan et al.[28] found that LECT2 directly contributes to skeletal muscle insulin resistance via the phosphorylation of Jun NH2-terminal kinase in myocytes. Combined with its role in hepatic inflammation and homeostasis, their findings suggests that LECT2 could mechanistically link liver disease and insulin resistance. To that point, Want et al.[27] recently found that LECT2 aggravated NAFLD in mice fed a high fat diet while inhibition of LECT2 expression alleviated disease via the signal transducers and activators of transcription-1 (STAT-1) pathway. These findings were confirmed in humans by Zhang et al., who found that LECT2 was significantly increased in those newly diagnosed with type 2 diabetes, and Yoo et al., who found increased circulating LECT2 in those with both type 2 diabetes and NAFLD.[33,34] Subsequently, Xu et al.[26] demonstrated the clear role of increased LECT2 in the progression of hepatic fibrosis as a ligand of Tie1. The current literature cannot fully distinguish between correlation and causation, thus further study is indicated. To that end, Hwang et al.[35] found that inhibition of LECT2 by dipeptidyl peptidase-IV (DPPIV) inhibitor was associated with improved hepatic steatosis and insulin resistance in mice fed a high fat diet. After confirming elevated LECT2 levels in adult humans and mice with NAFLD, Wang et al.[27] found that inhibition of LECT2 improved hepatic steatosis and inflammation in their mouse NAFLD model while LECT2 overexpression worsened steatosis and inflammation. Investigating pathways via RNA-sequencing and bioinformatic analysis, their group identified the STAT-1 pathway as an essential pathogenic step and proposed that an inhibitor of this pathway could be a future therapy.[27] While molecular mechanisms are not yet fully clear, there are published data suggesting an interplay between DPPIV and STAT-1, making this is a promising target for research.[36]

Future studies need to compare LECT2 to other potential biomarkers, either isolated or as part of a combined battery of tests. Fibroblast growth factor 21 (FGF21) is positively correlated with human hepatic steatosis independent of fasting status.[37] In addition to diagnostic abilities, there are several studies assessing the therapeutic potential of reversing FGF21 resistance to improve steatosis.[38] Inversely, adiponectin is an adipokine found to be decreased in NAFLD, leading to worsening hepatic lipid accumulation that has diagnostic potential.[39] Similar to FGF21, there are trials underway to increase circulating adiponectin itself or activation in its downstream targets to improve steatotic liver disease. Comparing and combining these biomarkers with others such as interleukin 6 has the potential to further improve diagnostic accuracy and personalize therapies.

Our study contributes to the growing body of evidence that LECT2 should be included in future research as a potential screening biomarker of pediatric steatotic liver disease. With calls to develop more non-surgical options for pediatric patients with NAFLD, including LECT2 in future studies could lead to more diagnostic and therapeutic strategies for a patient population that has some of the least number of available options.[13]

AUTHOR CONTRIBUTIONS

M.T.P., U.A., and V.S. designed the research. D.P.-C., D.R.R., L.K.H., M.T.P., J.T., S.A.W., U.A., and V.S. performed the research. D.P.-C., D.R.R., M.T.P., U.A., and V.S. analyzed the data. D.R.R., M.T.P., U.A., and V.S. wrote the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declared no competing interests for this work.

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