REVIEW DERLEME

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Relationship of Liver Enzymes to Homeostatic Model Assessment Insulin Resistance in Non-Alcoholic Fatty Liver Disease Patients: A Meta-Analysis and Systematic Review

Non Alkolik Yağlı Karaciğer Hastalarında Karaciğer Enzimleri ile İnsülin Direnci Homeostatik Model Değerlendirmesi İlişkisi: Bir Meta-Analiz ve Sistematik Derleme

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ABSTRACT Studies have assessed that the liver enzymes were proven having the association with insulin resistance (IR) in patients with liver disease; however, there were conflicting findings across the reports. The purpose of this study was to assess the association between liver enzymes and Homeostatic Model Assessment Insulin Resistance (HOMA-IR) in patients with non-alcoholic fatty liver disease (NAFLD). We conducted a meta-analysis between April 2022 and August 2022. Data were obtained from articles in PubMed, ScienceDirect, Cochrane Library, and Taylor & Francis. Using a Z test, the liver enzymes and the HOMA-IR among patients with NALD were compared. We included 683 patients with elevated liver enzymes and 3.579 patients with normal liver enzymes, retrieved from five papers. HOMA-IR score appeared higher in patients with NAFLD with elevated alanine aminotransferase (ALT) than in patients with normal ALT [ALT, mean difference (MD): 1.02; 95% confidence interval (CI): 0.49, 1.54]. Conversely, the aspartate aminotransferase (AST), alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT) had no crucial impact in affectting the HOMA-IR when compared between patients with NAFLD and control [(AST, MD: 0.81; 95% CI: 0.21, 1.40), (GGT, MD: 0.77; 95% CI: 0.20, 1.34), and (ALP, MD: 0.90; 95% CI: 0.22, 1.57)]. IR assessed using HOMA-IR has a significant association with abnormal liver enzymes in patients with NAFLD.

Keywords: Non-alcoholic fatty liver disease; homeostatic model assessment insulin resistance; liver enzymes

ÖZET Karaciğer hastalarında karaciğer enzimlerinin insülin direnci [insulin resistance (IR)] ile ilişkili olduğunun kanıtladığı, çalışmalarla değerlendirilmiştir. Ancak raporlar arasında birbiriyle çelişen bulgular mevcuttur. Bu çalışmanın amacı, non alkolik yağlı karaciğer hastalığı [non-alcoholic fatty liver disease (NAFLD)] hastalarında karaciğer enzimleriyle insülin direnci homeostatik model değerlendirmesi [homeostatic model assessment insulin resistance (HOMA-IR)] ilişkisini değerlendirmektir. Nisan 2022 ve Ağustos 2022 arasında bir meta-analiz gerçekleştirilmiştir. Veriler PubMed, ScienceDirect, Cochrane Library ve Taylor & Francis'de bulunan makalelerden elde edilmiştir. Z-testi kullanılarak NAFLD hastaları arasında karaciğer enzimleri ve HOMA-IR karşılaştırılmıştır. Beş makaleden elde edilen yüksek karaciğer enzimli 683 hasta ve normal karaciğer enzimli 3579 hasta çalışmaya dahil edilmiştir. HOMA-IR skoru, alanin aminotransferaz (ALT) değeri yüksek olan NAFLD hastalarında, ALT değeri normal olan hastalara kıyasla daha yüksek bulunmuştur [ALT, ortalama fark (OF): 1.02; 95% güven aralığı (GA) : 0.49, 1.54]. Buna karşılık, aspartat aminotransferaz (AST), alkalin fosfataz (ALP) ve gama-glutamil transferaz (GGT) NAFLD hastaları ve kontrol karşılaştırıldığında HOMA-IR'ı etkilemede önemli bir etkiye sahip değildi [(AST, OF: 0.81; 95% GA: 0.21, 1.40), (GGT, OF: 0.77; 95% GA: 0.20, 1.34), and (ALP, OF: 0.90; 95% GA: 0.22, 1.57)]. HOMA-IR kullanılarak değerlendirilen IR, NAFLD hastalarında anormal karaciğer enzimleri ile anlamlı bir ilişkiye sahiptir.

Anahtar Kelimeler: Non alkolik yağlı karaciğer hastalığı; insülin direnci homeostatik model değerlendirmesi; karaciğer enzimleri

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Almost one-quarter of adults worldwide suffer from non-alcoholic fatty liver disease (NAFLD).[1,2] A quarter of the world's population has NAFLD; the rate is lowest in Africa (13%), in Europe (23%), and highest in the Middle East (32%).[3] Type 2 diabetes mellitus (T2DM), central obesity, dyslipidemia, and metabolic syndrome have strong correlations with NAFLD, with relative prevalences were 23%, 51%, 69%, and 43%; respectively.[4-6] Therefore, as the prevalence of obesity increased, the cost of healthcare increased from 15% to 25% between 2005 and 2010.[7] NAFLD development is promoted by the metabolic illness of hepatic insulin resistance (IR).[8-12] Extensive research into the correlation between histology and clinical outcome in NAFLD patients has revealed that the presence of more markers of the metabolic syndrome increased the likelihood of fibrosis and severe illness.[13-16]

Because IR can lead to the production of free fatty acids (FFAs) from visceral adipose tissue and directly affect hepatic lipid metabolism, it has a strong correlation with fat gain.[17-19] Those at high risk for T2DM or obesity should not be systematically screened for NAFLD in primary care settings or hospitals. This is due in part to the fact that the diagnosis and management of NAFLD are still poorly understood, and also because a trustworthy screening test has not yet been established.[20-23] Homeostatic Model Assessment Insulin Resistance (HOMA-IR) is a rapid and cost-effective method to assess IR. However, the effectiveness of HOMA-IR in identifying T2DM patients with NAFLD is unknown clearly.[24-27]

Liver injury is often evaluated by measuring serum levels of liver enzymes, such as: alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), and alkaline phosphatase (ALP).[25-29] Despite the evidences had revealed the potential association between NAFLD and IR, the cause of liver damage in diabetic individuals remains a mystery, and neither high liver enzymes nor IR can be attributed to anything other than the disease itself.[30-34] The absence of effective therapies can also be attributed to a lack of understanding of these mechanisms. This study aimed to analyze the association between liver enzymes and HOMA-IR in patients with NAFLD.

MATERIAL AND METHODS

STUDY DESIGN

We conducted a meta-analysis to investigate the association between liver enzymes and IR in patients with NAFLD. Our study evaluated the liver enzymes: ALT, AST, ALP, and GGT. Meanwhile, IR was measured using HOMA-IR. Preferred Reporting Items for Systematic Review and Meta-Analysis was applied as the guidance of our study.[35]

ELIGIBILITY CRITERIA

Studies were included in our review if they met the following criteria: (1) assessed AST, ALP, GGT, ALT, and HOMA-IR in patients with NAFLD; (2) provided the required information to calculate the odds ratio and 95% confidence interval (CI); and (3) written in English. Reviews, nonstandard data presentations, low-quality papers, and studies with double publications were excluded from our study.

SEARCH STRATEGY AND DATA EXTRACTION

We started searching the data in PubMed, ScienceDirect, and Taylor and Francis on April 20, 2022. After carefully identifying the probable outcomes, a further search was done to find prospective papers that could be used in our study. The keywords were: "Liver Enzymes" or "alanine transaminase" or "aspartate transaminase" or "alkaline phosphatase" or "gamma-glutamyl transferase;" and "Homeostatic Model Assessment for Insulin Resistance" or "insulin resistance;" and "non-alcoholic fatty liver disease" or "non-alcoholic steatohepatitis". Only studies in English were included. In case of double publication was found, only the higher sample size articles were included. We also used the reference lists of related papers to find the additional articles. The following information was collected during data extraction: (1) author name and year, (2) study location, (3) sample size between normal liver enzymes and elevated liver enzymes, and (4) mean HOMA-IR. Using a pilot form, two independent researchers (LNP and PIDA) performed data extraction. We established a discussion if we found disagreement.

ASSESSMENT OF THE ARTICLE QUALITY

Before included in the statistical analysis, paper quality was assessed using the New Castle-Ottawa Scale. In this analysis, we assessed on how patients were selected, how different groups performed, and how much exposure each group received. Low quality papers received scores under 4, moderate quality papers received scores between 5 and 6, and high quality papers received scores above 7. The pilot form was used to conduct the study assessment by two independent researchers (LNP and PIDA). In the event of a disagreement, PIDA, another investigative team, was consulted.

STUDY MEASURES

The predictor variable in our study was liver enzymes in patients with NAFLD. The liver enzymes were ALT, ALP, GGT, and AST. AST and ALT were considered to be elevated if their values were >80 U/L. GGT was considered to be increased if its value was ≥40 U/L. Meanwhile, ALP was considered to be increased if its value was ≥280 U/L.[36,37] IR is the study's conclusion, however. The IR using the Homeostasis Model Assessment Index was used to determine if a subject was insulin resistant (HOMA-IR).[38]

STATISTICAL ANALYSIS

NAFLD patients with normal and elevated liver enzyme levels were compared using Z-tests, and the influence on the evaluation of IR was estimated using the odds ratio mean difference (MD) and 95% CI 95%. Before evaluating associations and effect estimates, we assessed the data for publication bias and study heterogeneity. Publication bias was evaluated using Egger's test. The p-value of less than 0.05 indicatedpublication bias. The Q test was also used to assess the degree of heterogeneity between studies. The p-value of less than 0.10 indicated that the heterogeneity was existed. The calculation in our meta-analysis was performed using comprehensive meta-analysis software (CMA, Chicago, USA).

RESULTS

THE ELIGIBLE STUDIES

A total of 8,487 potential studies were found, and 973 studies were excluded due to inappropriate titles and abstracts. We also reviewed the complete texts of 333 potential studies. Additionally, we eliminated articles because they were reviews (n=212), lacked sufficient data to calculate odds ratios and 95% CI (n=15), and had low-quality studies (n=101). Finally, our meta-analysis included 5 studies. Our study selection method is depicted in Figure 1, and the features of the studies are listed in Table 1. The association between liver enzymes and HOMA-IR is summarized in Table 2.

IR OF PATIENTS WITH NAFLD PREDICTED BY LIVER ENZYMES

From the 5 papers, we found that 4 liver enzymes were available for the meta-analysis. We discovered that patients with NAFLD who had elevated ALT scores had higher HOMA-IR scores than those with normal ALT levels (ALT, MD: 1.02; 95% CI: 0.49, 1.54). Moreover, the AST, ALP, and GGT had statistically no significant difference in influencing the HOMA-IR compared with patients with NAFLD who had normal AST, ALP, and GGT [(AST, MD: 0.81; 95% CI: 0.21, 1.40), (GGT, MD: 0.77; 95% CI: 0.20, 1.34), and (ALP, MD: 0.90; 95% CI: 0.22, 1.57)] (Figure 2, Figure 3, Figure 4, Figure 5).

SOURCE OF HETEROGENEITY

We found that all of the data including ALT, AST, GGT, and ALP scores were not uniformly distributed across the predictors. As a result, we used both fixed and random effects models in our analysis. Data for AST, ALP, and GGT were analyzed using fixed-effects models because heterogeneity was not supported by the available evidence. A random-effects model was adopted for analysis because there was evidence of clinical presentation variability in the ALT data.

POTENTIAL PUBLICATION BIAS

To assess the probability of publication bias, Egger's test and Risk of bias assessment using Cochrane risk of bias 2/RoB 2 tool was utilized (Figure 6). We did not find any evidence of publication bias for ALT, AST, GGT, or ALP at the 0.05 significance level.

DISCUSSION

Our findings corroborated the hypothesis that patients with NAFLD and elevated ALT had a greater

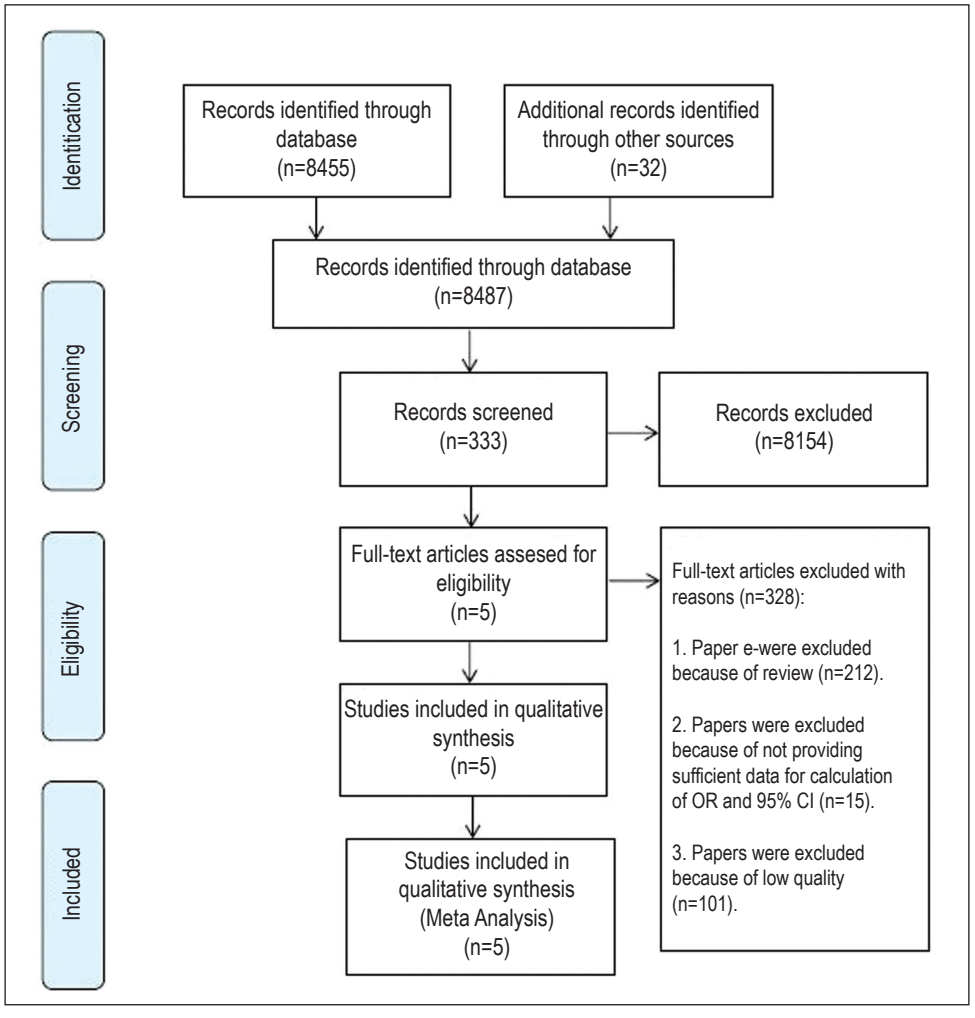

FIGURE 1: Flowchart for paper selection in our study.
OR: Odds ratio; CI: Confidence interval.

HOMA-IR than those with normal ALT. A meta-analysis in this area has not been performed; therefore, we cannot compare our results with those of other studies. Several investigations have found an association between obesity, IR, and T2DM; however, this association has been attributedto aberrant liver cell function. Prospective studies have found an association between elevated levels of liver enzymes like ALT and the development of T2DM in adults.[39] Because of the correlation between increased ALT and NAFLD, it is possible that the prospective relationship between ALT and T2DM reflects a cross-sectional association with IR or obesity. Notably, the assessment of IR has not been explored, despite the fact that prior research have linked between ALT and T2DM, and not obesity.[39,40] Our results were most easily explained by the fact that an increase in ALT is a reflection of adipose changes in the liver, which in turn are a reflection of the pathophysiological changes that occur before T2DM develops. Chronic hyperinsulinemia in animal models has been shown to predispose the liver to relative resistance to the action of insulin that inhibits gluconeogenesis. Insulin receptor substrate 2 expression was unaffected, and sterol regulatory element-binding protein 1c was up-regulated. Both circumstance indicates the resistance condition, andboosts triglyceride production.[40,41] The increased hepatic IR and accompanying hepatic fathave been linked to hyperinsulinemia via this pathway. However, ALT is a gluconeogenesis enzyme,

TABLE 1: Baseline characteristics of the studies included in our analysis.

				Sample size			
Author, year	**Country**	**City**	**Hospital**	**Normal ALT**	**Elevated ALT**	**Study setting**	**NOS**
Cankurtaran et.al, 2007[58]	Türkiye	Ankara	Hacettepe University Hospital	33	19	Normal vs. elevated ALT	9
Cekdemir et.al, 2019[59]	Türkiye	Manisa	Hafsa Sultan Celal Bayar University Hospital	40	26	Normal vs. elevated ALT	8
Esteghamati et.al, 2011[60]	Iran	Tehran	Vali-Asr Hospital	479	191	Normal vs. elevated ALT	9
Fracanzani et.al, 2008[61]	Italy	Milan	Hospital Maggiore Policlinico	63	395	Normal vs. elevated ALT	8
Sheng et.al, 2018[62]	China	Harbin	Second Affiliated Hospital of Harbin Medical University	14	69	Normal vs. elevated ALT	9
				Sample size			
Author, year	**Country**	**City**	**Hospital**	**Normal AST**	**Elevated AST**	**Study setting**	**NOS**
Cankurtaran et.al, 2007[58]	Türkiye	Ankara	Hacettepe University Hospital	33	19	Normal vs. elevated AST	9
Cekdemir et.al, 2019[59]	Türkiye	Manisa	Hafsa Sultan Celal Bayar University Hospital	40	26	Normal vs. elevated AST	8
Sheng et.al, 2018[62]	China	Harbin	Second Affiliated Hospital of Harbin Medical University	187	25	Normal vs. elevated AST	9
Author, year	Country	City	Hospital	Sample size	Study setting	NOS	
				Normal ALP	Elevated ALP		
Cankurtaran et.al, 2007[58]	Türkiye	Ankara	Hacettepe University Hospital	36	16	Normal vs. elevated ALP	9
Cekdemir et.al, 2019[59]	Türkiye	Manisa	Hafsa Sultan Celal Bayar University Hospital	40	26	Normal vs. elevated ALP	8
				Sample size			
Author, year	**Country**	**City**	**Hospital**	**Normal GGT**	**Elevated GGT**	**Study setting**	**NOS**
Cankurtaran et.al, 2007[58]	Türkiye	Ankara	Hacettepe University Hospital	28	24	Normal vs. elevated GGT	9
Cekdemir et.al, 2019[59]	Türkiye	Manisa	Hafsa Sultan Celal Bayar University Hospital	40	26	Normal vs. elevated GGT	8
Sheng et.al, 2018[62]	China	Harbin	Second Affiliated Hospital of Harbin Medical University	146	66	Normal vs. elevated GGT	9

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; GGT: Gamma-glutamyl transferase; NOS: New Castle-Ottawa Scale.

TABLE 2: Summary of the association between ALT, AST, GGT, ALP, and HOMA-IR.

				Value					
Outcomes	**NS**	**Model**	**Increased ALT**	**Normal ALT**	**pE**	**pHet**	**p value**	**MD**	**95% CI**
HOMA-IR	5	Random	4.84±2.342	3.792±1.796	0.40033	0.003	0.0001	1.02	0.49-1.54
				Value					
Outcomes	**NS**	**Model**	**Increased AST**	**Normal AST**	**pE**	**pHet**	**p value**	**MD**	**95% CI**
HOMA-IR	3	Fixed	5.39±2.37	4.24±2.603	0.36398	0.14	0.04	0.81	0.21-1.40
				Value					
Outcomes	**NS**	**Model**	**Increased GGT**	**Normal GGT**	**pE**	**pHet**	**p value**	**MD**	**95% CI**
HOMA-IR	3	Fixed	4.98±2.446	4.176±2.59	0.55624	0.68	0.008	0.77	0.20-1.34
				Value					
Outcomes	**NS**	**Model**	**Increased ALP**	**Normal ALP**	**pE**	**pHet**	**p value**	**MD**	**95% CI**
HOMA-IR	2	Fixed	4.255±1.8	3.335±1.725	0.193	0.60	0.009	0.90	0.22-1.57

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: Gamma-glutamyl transferase; ALP: Alkaline phosphatase; HOMA-IR: Homeostatic model assessment insulin resistance; MD: Mean difference; CI: Confidence interval.

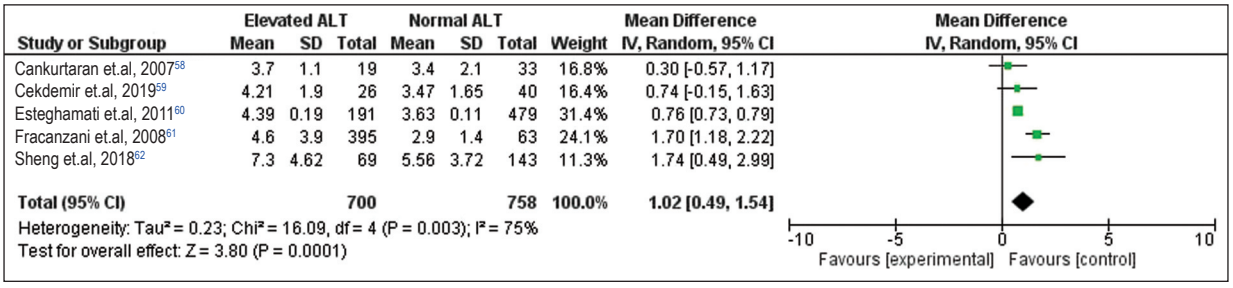

FIGURE 2: Forest plot of the association between ALT and HOMA-IR in patients with NAFLD.
ALT: Alanine aminotransferase; HOMA-IR: Homeostatic model assessment insulin resistance; NAFLD: Non-alcoholic fatty liver disease; SD: Standard deviation; CI: Confidence interval; df: Degree of freedom.

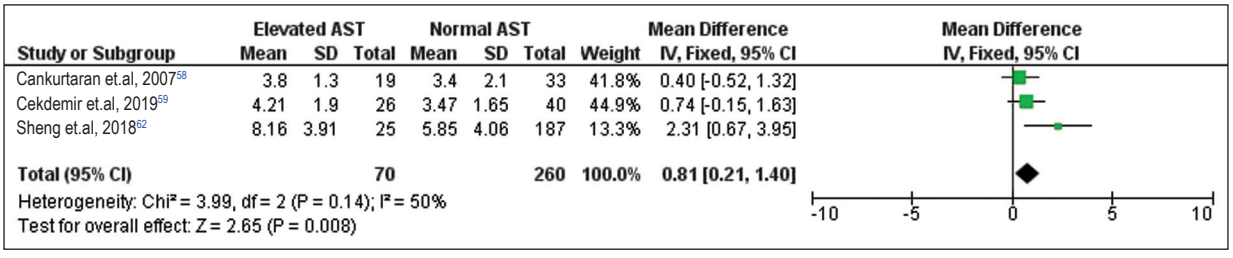

FIGURE 3: Forest plot of the association between AST and HOMA-IR in patients with NAFLD.
AST: Aspartate aminotransferase; HOMA-IR: Homeostatic model assessment insulin resistance; NAFLD: Non-alcoholic fatty liver disease; SD: Standard deviation; CI: Confidence interval; df: Degree of freedom.

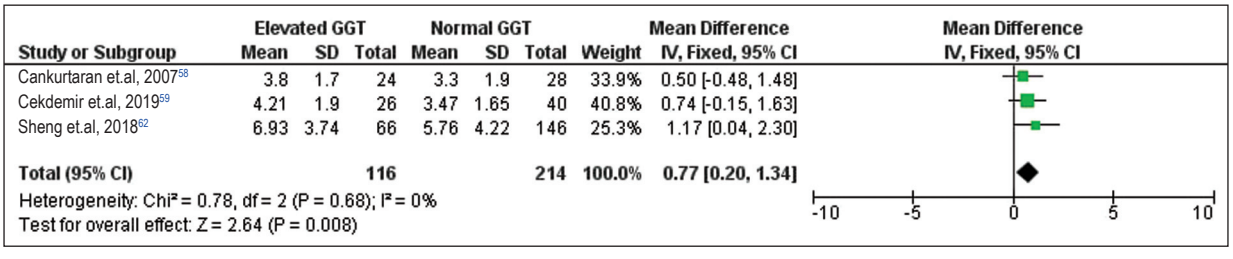

FIGURE 4: Forest plot of the association between GGT and HOMA-IR in patients with NAFLD.
GGT: Gamma-glutamyl transferase; HOMA-IR: Homeostatic model assessment insulin resistance; NAFLD: Non-alcoholic fatty liver disease; SD: Standard deviation; CI: Confidence interval; df: Degree of freedom.

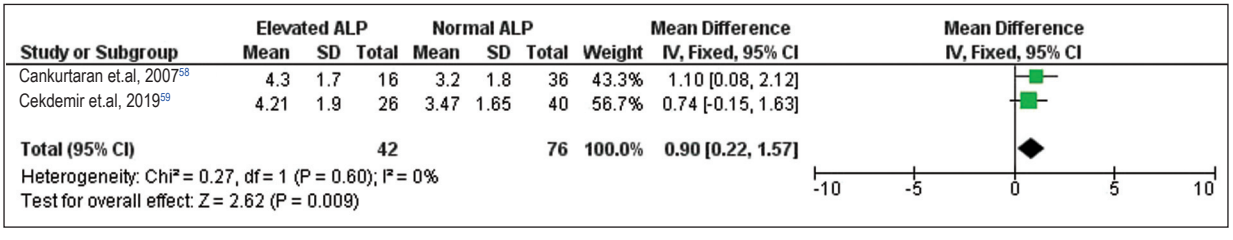

FIGURE 5: Forest plot of the association between ALP and HOMA-IR in patients with NAFLD.
ALP: Alkaline phosphatase; HOMA-IR: Homeostatic model assessment insulin resistance; NAFLD: Non-alcoholic fatty liver disease; SD: Standard deviation; CI: Confidence interval; df: Degree of freedom.

and insulin inhibits genes encoding gluconeogenesis enzymes; hence, elevated ALT levels may be indicative of defective insulin signaling rather than necessarily indicating liver disease.[42] Possible explanations for ALT's ability to predict future T2DM in Pima Indians rather than more direct measurements of hepatic insulin sensitivity, such as hepatic glucose output, include methodological problems in assessing hepatic glucose production using radiotracer techniques.[42] The association between chronic inflammation and T2DM risk factors in later life suggests a secondary pathophysiological mechanism.[43,44] When

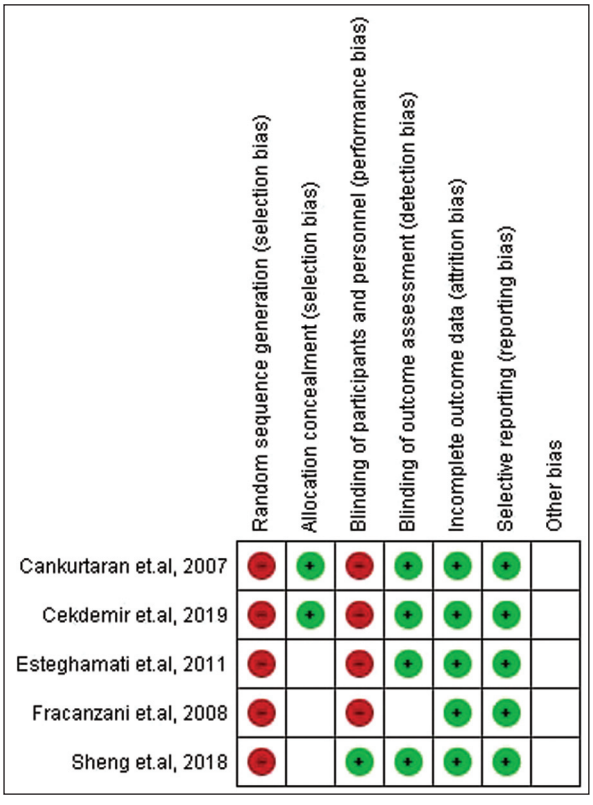

FIGURE 6: The risk of bias.

the liver is exposed to the proinflammatory cytokine tumor necrosis factor, it often responds with fatty alterations. Consequently, alterations in fat and concurrent ALT elevations might be indicative of inflammation, which disrupts insulin communication in the liver and elsewhere in the body.[45]

Our findings also revealed that elevated AST, GGT, and ALP had no significant difference in influencing the HOMA-IR compared with patients with NAFLD who had normal AST, ALP, and GGT. Because of this dearth data, it is not possible to conduct a comprehensive meta-analysis of the association between AST, GGT, and ALP in NAFLD patients at this time. Previous study on AST agreed with our findings, however study on GGT did not. IR was found to be strongly associated to increase ALT levels, but not increased AST levels, in a study of 1732 young adults aged 18 to 23.[46] Gray et al. studied 40 overweight and obese individuals without T2DM, and they revealed a strong association between IR and GGT.[47] After taking into account other factors that could have played a role, IR was found to be related with GGT in patients with NAFLD.[48] Bradley et al, in a study with 6,814 individuals, evaluated the continuous association between GGT and HOMA-IR, and they found a positive correlation when controlling for confounding factors.[49] In addition to abdominal obesity and obesity, it appears that a small increase in GGT activity within the normal range is a powerful predictor of IR.[50] The association between GGT and IR may have its origins in oxidative stress and the function of cellular GGT in the metabolism of extracellular reduced glutathione. It is believed that cellular GGT contributes to the production of reactive oxygen species when iron or other transition metals are present.[50,51] Since oxidative stress is linked to IR, serum GGT may be observed as a sensitive enzyme in this context.[52] However, there was no correlation between lower hepatic or systemic insulin action or AIR and higher levels of baseline AST and ALP. Liver dysfunction is addressed as a possible etiological factor in the later onset of T2DM.[53] Animal studies in which interruption of insulin transmission to the liver results in T2DM provide further support for the hypothesis that isolated hepatic IR contributes to broader poor glucose tolerance.[53] ALP and bilirubin were found to have a strong positive association by HOMA-IR.[54] Higher IR-related hepatic enzyme activity lends credence to this observation.[55] IR and liver disease have been studied, and the double hit hypothesis may shed light on how this happens. First, steatosis develops; then, a second blow-an oxidative stressor like a high-fat diet-increases CYP2E1 and intrahepatic FFA concentrations, leading to dramatic lipid peroxidation.[56] In both the fasting and fed stages, patients with NAFLD have elevated rates of de novo lipogenesis, and adipose tissue blunts the antilipolytic impact of insulin by raising the rate of basal lipolysis in adipocytes, which in turn increases fatty acid delivery to the liver.[57-59] Hepatic oxidative stress is further exacerbated by IR, which in turn upregulates CYP2E1 to boost hepatic fat deposition.[60]

Our current study is the first meta-analysis investigating the association between liver enzymes and HOMA-IR in patients with NAFLD. As widely known that the general population is increasingly engaging in annual checkups for early disease identification and health promotion. We know that the

process has a long pathway and may require a lot of cost. By implementing the results of our study, the process may be streamlined, suggesting that individuals at high risk for NAFLD can be identified earlier and more efficiently. However, future study by combining liver enzymes and other standard measurements of IR may allow for considerable better association of HOMA-IR in patients with NAFLD.

Our present study had several important limitations. First, the potential possible confounding factors, such as age, gender, race, nutritional status, comorbidiry, family history, and environmental factors were not assessed. Second, our analysis may yield little evidence because the design of included studies in our analysis was non-RCT. Third, even we performed a pooled calculation, the posibility of false positives findings should be the caution due to limited sample size. Hence, further study-with larger sample size is needed to investigate this study context.

CONCLUSION

Our results demonstrate a strong association between HOMA-IR and elevated liver enzymes in NAFLD patients. Our findings also imply that IR can be used as a biomarker to identify individuals at high risk for abnormalities in liver function,and the treating IR with lifestyle changes or pharmaceuticals may be effective to prevent disease development.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Putu Ijiya Danta Awatara, Jonny Karunia Fajar, Syifa Mustika;* ***Design:*** *Putu Ijiya Danta Awatara, Jonny Karunia Fajar, Syifa Mustika;* ***Control/Supervision:*** *Putu Ijiya Danta Awatara, Jonny Karunia Fajar, Syifa Mustika;* ***Data Collection and/or Processing:*** *Putu Ijiya Danta Awatara, Levrita Nindya Poerti;* ***Analysis and/or Interpretation:*** *Putu Ijiya Danta Awatara, Levrita Nindya Poerti;* ***Literature Review:*** *Putu Ijiya Danta Awatara, Levrita Nindya Poerti;* ***Writing the Article:*** *Putu Ijiya Danta Awatara, Levrita Nindya Poerti, Jonny Karunia Fajar;* ***Critical Review:*** *Putu Ijiya Danta Awatara, Jonny Karunia Fajar, Syifa Mustika;* ***References and Fundings:*** *Putu Ijiya Danta Awatara, Levrita Nindya Poerti, Jonny Karunia Fajar, Syifa Mustika;* ***Materials:*** *Putu Ijiya Danta Awatara, Jonny Karunia Fajar, Syifa Mustika.*

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