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Risk factors for liver fibrosis progression from early stage to late stage in nonalcoholic fatty liver disease: a systematic review and meta-analysis

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Abstract: *OBJECTIVE: The risk factors of fibrosis progression from an early stage to a late stage in non-alcoholic fatty liver disease were systematically analyzed, providing evidence for clinical workers to identify, intervene and block the progression of liver fibrosis in patients at an early stage.METHODS: The author independently used PubMed for a literature search on November 21, 2022. Two researchers independently screened the literature and cross-checked it. Any disputes were resolved by consulting the third researcher. The quality of the literature was evaluated using the Newcastle Ottawa Sca, and Then perform statistical analysis through Review Manager 5.4.RESULTS: Nine kinds of literature were included in this study. A meta-analysis of 11 factors associated with advanced fibrosis in patients with early-stage of nonalcoholic fatty liver disease showed that 5 factors were statistically significant, namely diabetes mellitus (OR=4.04, 95%CI 1.51-10.82, P=0.006). High body mass index (MD=1.89, 95%CI 0.78-3.00, P=0.0009); Low platelet count (MD=-45.05, 95%CI -66.49-(-23.26), P=0.0001); High levels of aspartate aminotransferase (MD=14.92, 95%CI 8.53-21.31, P=0.00001); Low serum albumin (MD=-0.37, 95%CI-0.62-(-0.12), P=0.004). CONCLUSIONS: This study found that diabetes mellitus, high body mass index, low platelet count, high aspartate aminotransferase levels, and low serum albumin may be major risk factors for early fibrosis progression in NAFLD.*

Keywords: *Nonalcoholic fatty liver disease liver fibrosis; Early liver fibrosis; Advanced liver fibrosis; Risk factors; Meta-analysis*

1. Introduction

Liver fibrosis is a response to chronic liver injury caused by various factors, such as alcohol consumption, viral hepatitis, autoimmune hepatitis, non-alcoholic fatty liver disease (NAFLD), and cholestasis[1, 2], is the result of abnormal extracellular matrix (ECM) deposition[1].Liver fibrosis is a dynamic process. Early-stage fibrosis is usually treatable, while late-stage fibrosis has very limited effective treatment[3].Therefore, it is particularly important to predict the risk factors for late-stage liver fibrosis and thus halt its progression from early to late-stage fibrosis. Effective treatment of advanced liver fibrosis is very limited.

Existing studies have identified numerous risk factors for the progression from early to advanced fibrosis in patients with NAFLD liver fibrosis, such as diabetes, hypertension, high cholesterol, and low platelet count[4, 5].However, none of these factors have been systematically analyzed to provide a comprehensive evidence-based medical evaluation of the progression of NAFLD liver fibrosis. In this study, a systematic review and meta-analysis of patients with NAFLD liver fibrosis progressing from early to late stages were conducted to identify their risk factors and provide a basis for early identification and intervention by clinical practitioners.

2. Method

2.1 Search Strategy.

The PubMed database was systematically searched to identify eligible studies up to November 1,

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2022. The database was accessed by searching the PubMed website, and then searching keywords "Non-alcoholic Fatty Liver Disease", "hepatic fibrosis", "liver fibrosis" and "risk factor" on the home page to search. All references identified as relevant publications are reviewed for further research.

2.2 Exclusion Criteria and Inclusion Criteria.

Inclusion criteria: (1) Retrospective cohort studies and case-control trial studies. (2) Complete data are available in the literature with clear results. (3) The study population was patients with early-stage fibrosis (Progressive fibrosis with massive fibrous septa and a small amount of cirrhosis) in NAFLD diagnosed at various healthcare facilities, either by clinical, imaging, or liver biopsy diagnosis. (4) The outcome of the study is advanced liver fibrosis (A large amount of fibrous septum, a small amount of cirrhosis).

Exclusion criteria: (1) Individual reports, reviews, experimental animal studies, master's theses, and cross-sectional studies. (2) Incomplete data and unclear study results. (3) Studies reporting duplicate patient cohorts.

2.3 Data Extraction and Quality Evaluation of Literature.

Literature that met inclusion criteria was extracted from each study by two independent reviewers using standardized data collection forms. Extractions included first author, year/time of publication, country of study, study design, risk factors, number of patients with early-stage liver fibrosis, and number of patients with advanced liver fibrosis in NAFLD.

Two investigators independently assessed the quality of the included literature using the Newcastle Ottawa Scale (NOS). The literature was evaluated separately into two categories: cohort studies and case-control studies, and if disagreements arose, they were resolved by consulting a consensus of a third investigator. This quality assessment has 3 aspects (selection, comparability, and outcome) with a total of 8 items.

2.4 Data Analysis.

We used Review Manager 5.4 for meta-analysis of fixed or random effects models and plotted forest plots. Measures were expressed as weighted mean differences (MD) and 95% confidence intervals (95%CI), and counts were expressed as ratio (OR) and 95% confidence intervals (95%CI). Both used the I^2 test to assess study heterogeneity, with less heterogeneity when $I^2 \leq 50\%$ and a fixed effects model for statistical analysis, and more heterogeneity when $I^2 > 50\%$ and a random effects model for analysis. Forest plot analysis results with a combined effects test value of $P < 0.05$ indicated that the risk factor was statistically significant. Risk factors with large and statistically significant heterogeneity were subjected to sensitivity analysis to determine their stability, and the sources of heterogeneity were determined by subgroup analysis, and risk factors that were included in more than three studies in the literature and were statistically significant were plotted in funnel plots for publication bias tests.

3. Result

3.1 Literature Search Results

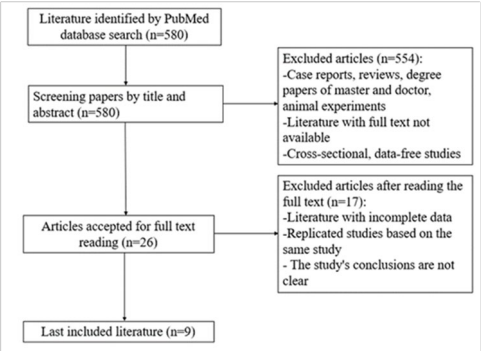

Figure 1: Literature screening flow chart.

ISSN 2706-6819 Vol.5, Issue 6: 34-45, DOI: 10.25236/IJFM.2023.050607

An initial search in the PubMed database as shown in Figure 1 yielded 580 papers, and 554 papers were excluded by reading the titles and abstracts, leaving 26 remaining papers. The remaining 26 articles were read in full text and 17 articles were excluded, and finally, 9 articles were included in this meta-analysis.

3.2 Included Study Characteristics and Quality Evaluation

A total of nine papers were included in this meta-analysis ([6-14]), with two studies each from the United Kingdom, Japan, and Korea, and one each from Spain, Poland, and Australia. A total of 2411 patients with NAFLD were included, of which 1974 patients had early liver fibrosis and 437 patients developed advanced liver fibrosis. The basic characteristics are shown in Table 1.

Table 1: Basic characteristics and NOS scores of the included literatures.

Study	Year	Nation	Study type	Advanced liver fibrosis/early liver fibrosis	Risk factors	NOS score
Dae Won Jun	2016	Korea	cohort studies	60/268	1,2,3,4,5,6,7,8,9,11,12	7
Gordon J-H Park	2011	Australia	case control study	23/25	1,2,3,4,5,7,8,10	5
Halina Cichoż-Lach	2012	Poland	cohort studies	27/99	1,2,3,6,7,8	6
Hye Won Lee	2017	Korea	case control study	60/1118	1,2,8,7,9,10,11	8
Kazuhisa Kodama	2019	Japan	case control study	69/35	1,2,3,6,7,8,9,10	7
Keisuke Kakisaka	2018	Japan	case control study	63/62	1,2,3,5,8	7
Sara Gómez de la Cuesta	2017	Spain	case control study	6/70	1,2,3,5,7,8,11	8
Stuart McPherson	2014	UK	case control study	55/230	1,2,3,4,5,6,8	8
V. Subramanian	2013	UK	cohort studies	74/67	1,2,4,5,7,10,11	6

Note: Risk factor 1. Male 2. High body mass index 3. High levels of aspartate aminotransferase 4. High triglycerides 5. High cholesterol 6. Diabetes 7. Low serum albumin 8. Low platelet count 9. High blood pressure 10. High bilirubin 11. Low HDL cholesterol

The quality ratings of the nine papers were assessed by using NOS to determine their high or low quality and the results of the ratings are shown in Table 1. It is clear from the table that all nine papers scored 5 and above, Quality meets the requirements of this study.

3.3 Results of Meta-analysis

3.3.1 Gender

Eight studies included in the research literature all suggested that progression from early to advanced fibrosis in patients with NAFLD liver fibrosis was associated with male factors and univariate analysis was performed, and pooled data from these studies showed a combined effect value OR=0.65, 95% CI (0.29-1.45); I^2=84%, with a large heterogeneity, and statistical analysis using a random effects model. The combined effect test value P=0.3 was not statistically significant. It is suggested that male is not a factor in the progression from early to late stage in patients with NAFLD fibrosis. Corresponding forest plots are shown in Figure 2.

3.3.2 Complications

Showed a large heterogeneity with OR=4.04, 95% CI (1.51-10.82), and I^2=84%, analyzed using a random effects model. The combined effects test showed P=0.006, which was statistically significant, suggesting that diabetes was a factor in the progression from early to late stage in patients with NALFD

ISSN 2706-6819 Vol.5, Issue 6: 34-45, DOI: 10.25236/IJFM.2023.050607

fibrosis. Corresponding forest plots are shown in Figure 3. There were three references to hypertension and the pooled data showed OR=1.35, 95% CI (0.92-1.99), I^2=25% heterogeneity, and random effects model analysis was used. The combined effects test showed P=0.13, which was not statistically significant. It is suggested that hypertension was not a factor in the progression from early to late stage in patients with NALFD fibrosis. Corresponding forest plots are shown in Figure 4.

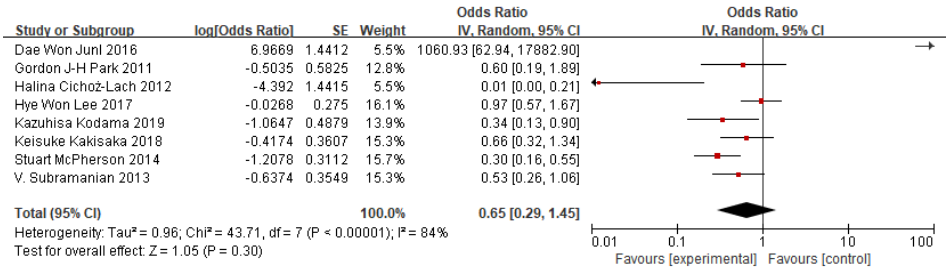

Figure 2: Forest map of Meta-analysis (male).

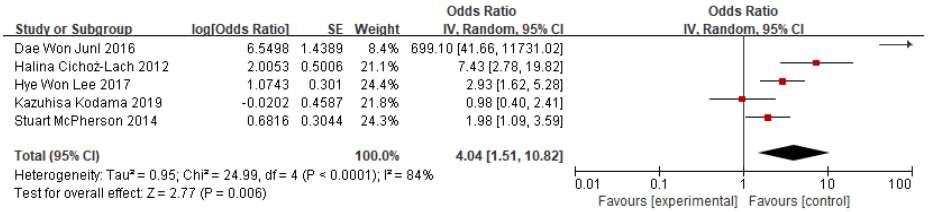

Figure 3: Forest map of meta-analysis (diabetes).

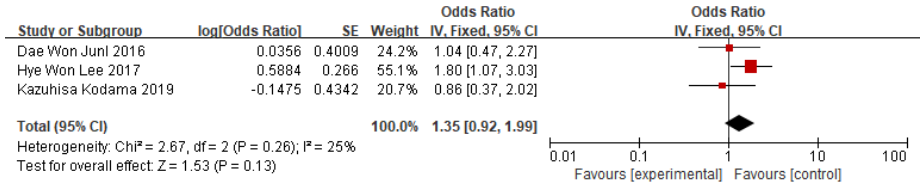

Figure 4: Forest map of Meta-analysis (hypertension).

3.3.3 Indicators Related to Hyperlipidemia

We performed univariate analysis to include clinical indicators such as high triglycerides, high levels of bilirubin, low levels of HDL cholesterol, and high cholesterol in the study to determine whether the above factors are risk factors for progression from early to advanced fibrosis in patients with fibrosis in NAFLD.

Four of the included studies in the research literature mentioned high triglycerides and the pooled data showed a large heterogeneity of MD=0.07, 95% CI (-0.82-21.31), I^2=72%, analyzed using a random effects model. The combined effects test showed P=0.92, which was not statistically significant. It is suggested that high triglyceride is not a factor in the progression from early to late stage in patients with fibrosis in NAFLD. Corresponding forest plots are shown in Figure 5.

Five studies in the included research literature mentioned high levels of bilirubin, and the pooled data showed MD=-0.05, 95% CI (-0.45-0.35), I^2=93%, and there was a large heterogeneity among these five studies in this analysis, which was analyzed using a random-effects model. The combined effects test showed P=0.80, which was not statistically significant. It is suggested that high levels of bilirubin are not a factor in the progression from early to late stages in patients with fibrosis in NAFLD. The corresponding forest plot is shown in Figure 6.

Four of the included studies in the research literature referred to low levels of HDL cholesterol, and the pooled data showed low heterogeneity with MD=-0.11, 95% CI (-0.23-0.01), and I^2=42%, which was analyzed using a fixed-effects model. The combined effects test showed P=0.07, which was not statistically significant. It is suggested that a low level of HDL cholesterol is not a factor in the progression from early to late stage in patients with fibrosis in NAFLD. Corresponding forest plots are shown in Figure 7.

Three of the included studies in the research literature mentioned high cholesterol, and pooling the data across studies showed MD=-7.77, 95% CI (-20.82-5.21), and I^2=66%, which showed a large

ISSN 2706-6819 Vol.5, Issue 6: 34-45, DOI: 10.25236/IJFM.2023.050607

heterogeneity among the three studies, using a random effects model. The combined effects test showed P=0.24, which was not statistically significant. It is suggested that high cholesterol is not a factor in the progression from early to late stages in patients with fibrosis in NAFLD. Corresponding forest plots are shown in Figure 8.

Our findings suggest that hyperlipidemia, although playing a very important role in the process of hepatic steatosis, may not be a major factor in the progression of liver fibrosis from early to late stages.

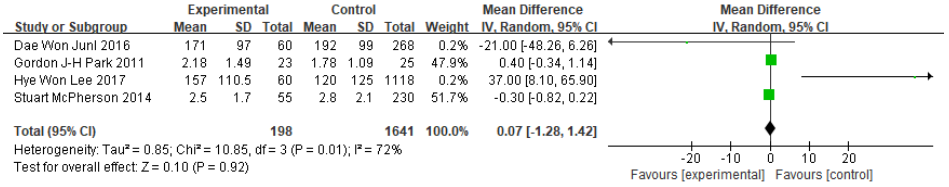

Figure 5: Forest map of meta-analysis (high triglycerides).

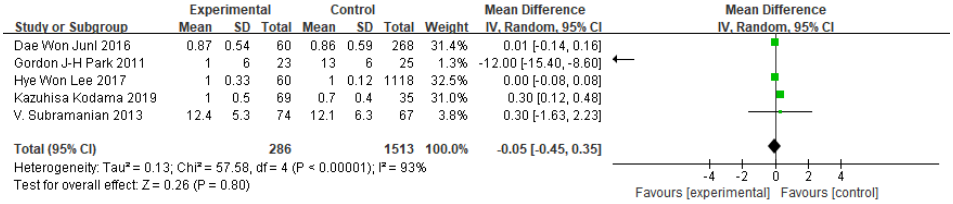

Figure 6: Forest map of meta-analysis (low level bilirubin).

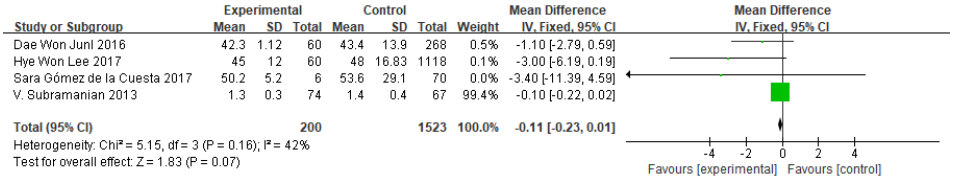

Figure 7: Forest map of meta-analysis (low level HDL cholesterol).

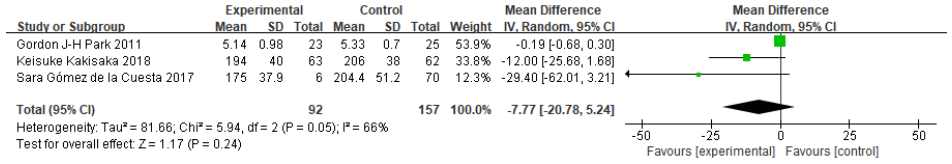

Figure 8: Forest map of meta-analysis (high cholesterol).

3.3.4 Other Clinical Predictors

We included high body mass index, high levels of aspartate aminotransferase, low serum albumin, and low platelet count indicators in the study as well to determine whether these factors are risk factors for progression from early to advanced fibrosis in patients with fibrosis in NAFLD.

All nine studies included in the literature mentioned high body mass index, and the pooled data from these studies showed a combined effect value MD=1.89, 95% CI (0.78-3.00); I^2=74% heterogeneity was large and analyzed using a random-effects model. The combined effects test showed P=0.0009, which was statistically significant. It is suggested that a high body mass index is a factor in the progression of NAFLD fibrosis patients from early to late stages. Corresponding forest plots are shown in Figure 9.

High levels of aspartate aminotransferase were mentioned in seven of the included studies in the literature, and the pooled data from these studies showed a low MD=14.92, 95% CI (8.53-21.31), I^2=39% heterogeneity, and were analyzed using a fixed-effects model. The combined effects test showed P=0.00001, which was statistically significant. It is suggested that a high level of aspartate aminotransferase is a factor in the progression from early to late stage in patients with NAFLD fibrosis. Corresponding forest plots are shown in Figure 10.

Seven of the included studies in the research literature mentioned low serum albumin, and the pooled data showed MD=-0.37, 95% CI (-0.62-(-0.12)), I^2=86% heterogeneity, and were analyzed using a random-effects model. The combined effects test showed P=0.004, which was statistically significant. It is suggested that low serum albumin is a factor in the progression from early to late stage in patients with

ISSN 2706-6819 Vol.5, Issue 6: 34-45, DOI: 10.25236/IJFM.2023.050607

fibrosis in NAFLD. Corresponding forest plots are shown in Figure 11.

Eight of the included studies in the research literature mentioned low platelet counts and the pooled data showed a large heterogeneity of MD=-45.05, 95% CI (-66.49-(-23.26)), I^2=91%, analyzed using a random-effects model. The combined effects test showed P=0.0001, which was statistically significant. It is suggested that low platelet count is a factor in the progression from early to late stage in patients with fibrosis in NAFLD. Corresponding forest plots are shown in Figure 12.

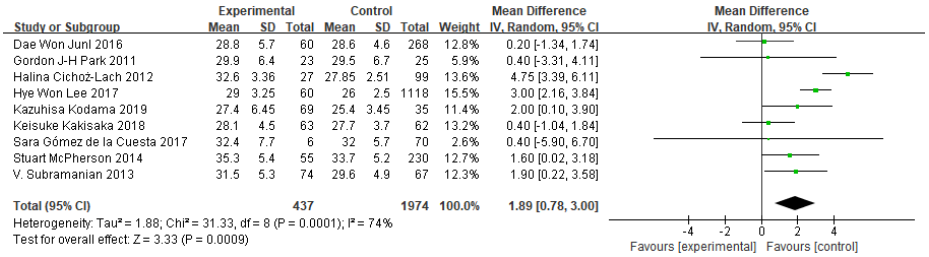

Figure 9: Forest map of meta-analysis (high body mass index).

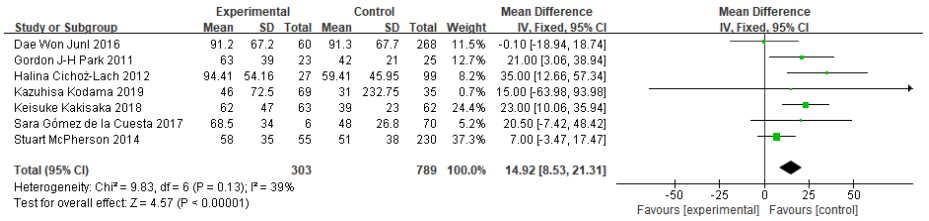

Figure 10: Forest map of meta-analysis (high level of aspartate aminotransferase).

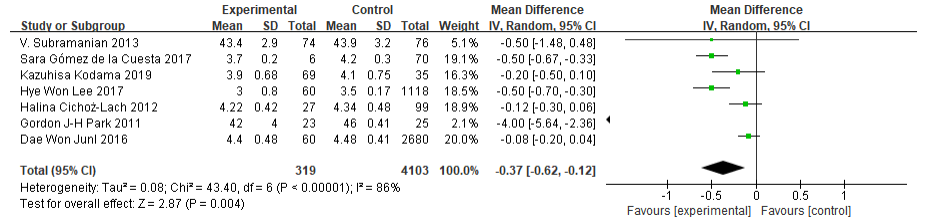

Figure 11: Forest map of meta-analysis (low serum albumin).

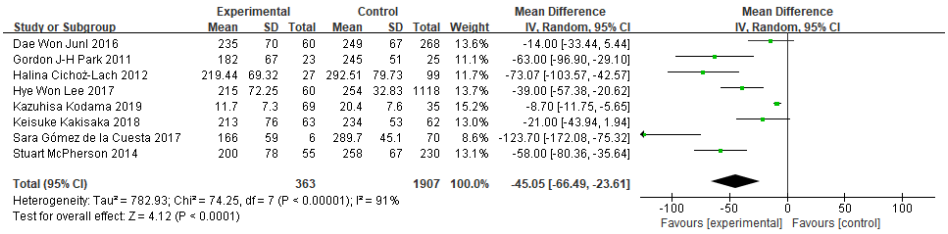

Figure 12: Forest map of meta-analysis (low platelet count).

3.4 Sensitivity Analysis

Diabetes mellitus, high body mass index, low serum albumin, and low platelet count were found to be statistically significant by univariate analysis, but with I^2 > 50%, heterogeneity was too great, so we performed sensitivity analyses for these risk factors. We excluded each study in each meta-analysis for diabetes, high body mass index, low serum albumin, and low platelet count in turn, and the differences between their findings and those of the univariate analysis were found to be small after the exclusion, and the combined effect test values were all P < 0.05, and no substantial differences were found, indicating that the stability of the analysis results was good.

3.5 Subgroup Analysis

We further performed a subgroup analysis of risk factors such as diabetes mellitus, high body mass index, low serum albumin, and low platelet count with large heterogeneity to determine the source of

ISSN 2706-6819 Vol.5, Issue 6: 34-45, DOI: 10.25236/IJFM.2023.050607

their large heterogeneity. The subgroup analysis revealed that age may be a source of heterogeneity for the risk factor of diabetes mellitus, and the corresponding forest is shown in Figure 13; alanine aminotransferase (ALT) level may be a source of heterogeneity for the risk factor of high body mass index, and the corresponding forest is shown in Figure 14; the high or low NOS score may be a source of heterogeneity for the risk factor of serum albumin, and the corresponding forest is shown in Figure 15. For the risk factor of low platelet count, after we excluded the paper Sara Gómez de la Cuesta 2017, we found that the high or low NOS score could be the source of heterogeneity, and the corresponding forest plot is shown in Figure 16.

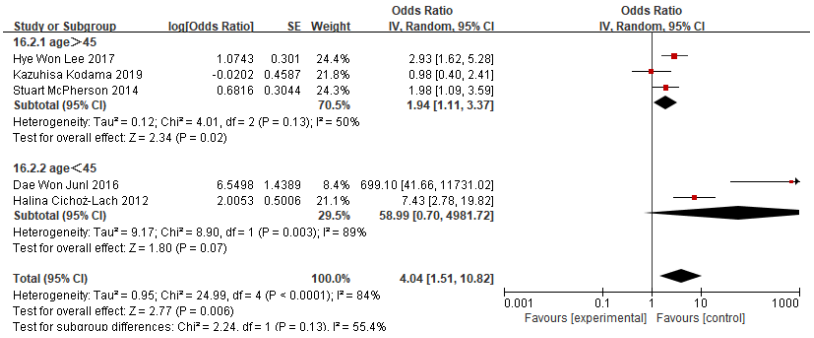

Figure 13: Subgroup analysis diagram (diabetes mellitus).

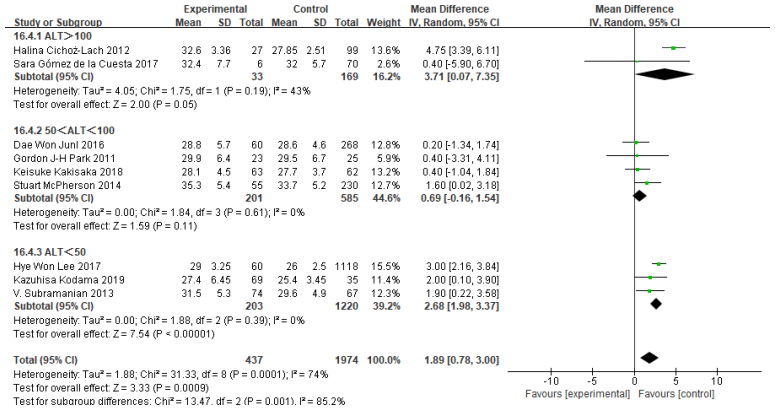

Figure 14: Subgroup analysis (high body mass index).

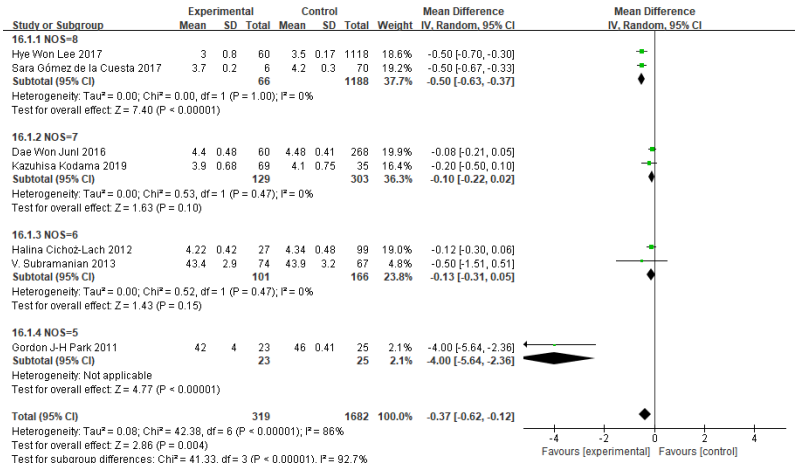

Figure 15: Subgroup analysis (low serum albumin).

ISSN 2706-6819 Vol.5, Issue 6: 34-45, DOI: 10.25236/IJFM.2023.050607

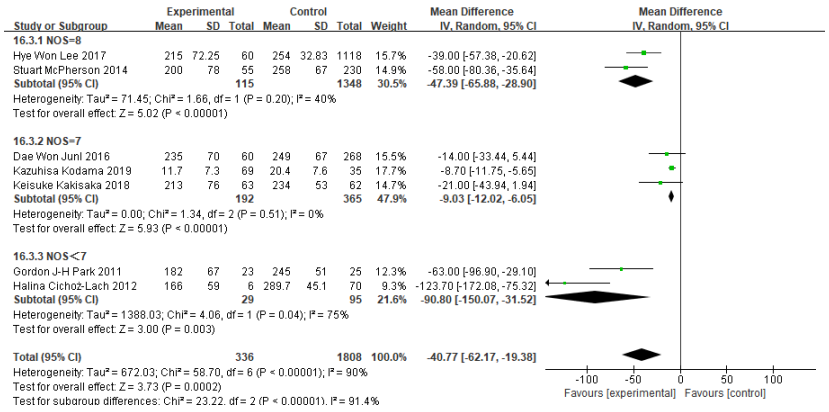

Figure 16: Subgroup analysis (low platelet count).

3.6 Publication Bias Analysis

Plotting studies with statistically significant risk factors diabetes, high body mass index, low serum albumin, low platelet count, and high levels of aspartate aminotransferase in a funnel plot for publication bias testing showed that the left-right distribution of each study site was largely symmetrical, indicating a low likelihood of publication bias, as shown in Figure 17.

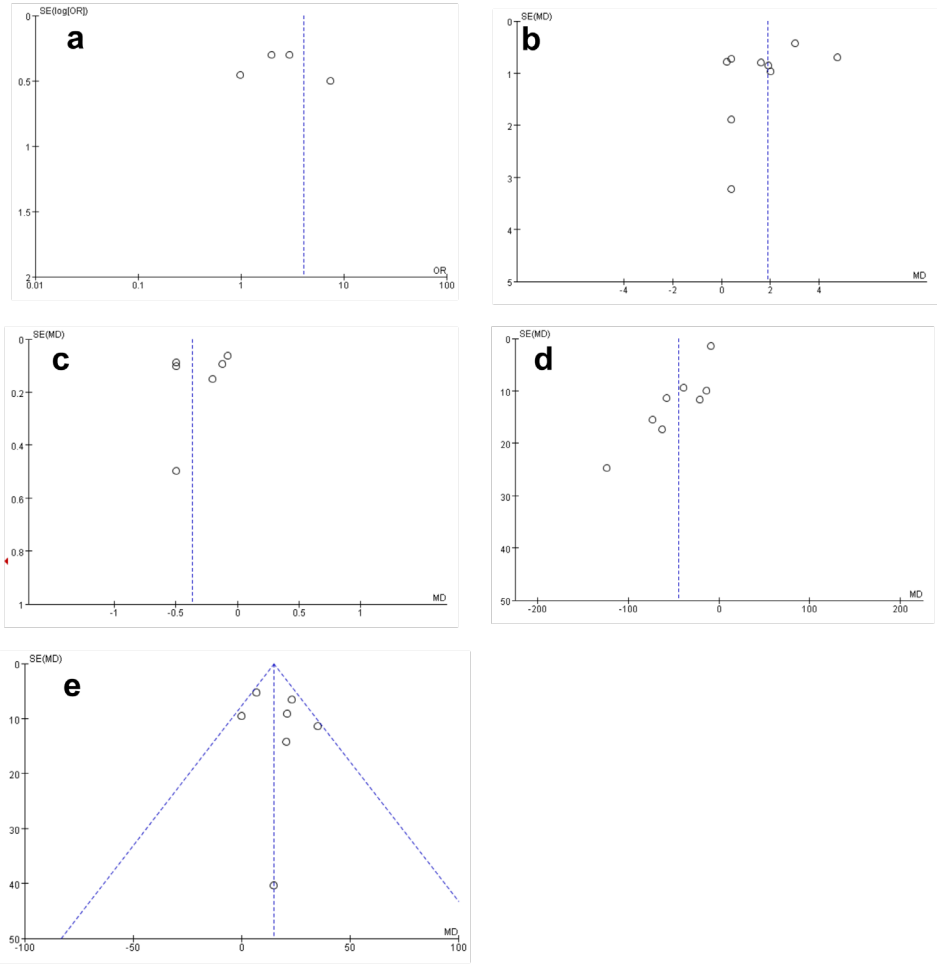

Figure 17: Funnel plot of each risk factor, a (diabetes), b (high body mass index), c (low serum albumin), d (low platelet count), e (high levels of aspartate aminotransferase).

ISSN 2706-6819 Vol.5, Issue 6: 34-45, DOI: 10.25236/IJFM.2023.050607

4. Discussion

Patients with NAFLD are often accompanied by a hepatic fibrosis process, and this study identified risk factors for progression from early to advanced stages of fibrosis in patients with NAFLD by analyzing the relationship between the two as diabetes, high body mass index, low serum albumin, low platelet count, and high levels of aspartate aminotransferase, respectively.

Diabetes mellitus and liver fibrosis are interconnected and mutually reinforcing. Under normal conditions, insulin increases glucose transporter (GLUT) receptor-mediated glucose uptake into hepatocytes, and in hepatic steatosis, hepatocytes have impaired glucose uptake and utilization, resulting in higher blood glucose concentrations in the liver. In turn, hyperglycemia can cause hepatocyte injury, resulting in the activation of macrophages (KCs) in the hepatic blood sinusoids and the overproduction of inflammatory cytokines that activate hepatic stellate cells, thereby inducing liver fibrosis[15]. It has been shown that diabetes promotes the progression of liver fibrosis in NAFLD and that patients with diabetes have a significant risk of advanced liver fibrosis[16].Patients with fibrosis in NAFLD with diabetes have a 67.3% probability of developing advanced fibrosis[15],[17].Patients with fibrosis in NAFLD with diabetes have a 67.3% probability of developing advanced fibrosis[18], concluded that diabetes is a risk factor for liver fibrosis progression and overall mortality in patients with NAFLD. All these studies are generally consistent with the results of the present study.

High body mass index is one of the clinical indicators to judge the degree of obesity, and obesity is closely related to the prevalence of NAFLD and the degree of liver fibrosis. Obese people become the main energy supply substance of the body due to the increase of adipose tissue in the body and the release of fatty acids and free fatty acids in the body, while the utilization of glucose decreases, which easily causes insulin resistance and a large number of fatty acids enter the liver to synthesize triglycerides and deposit to form Fatty liver, which in turn develops into liver fibrosis[19]. Magnus Hedenstierna et al[20]. ffound that a body mass index ≥25 kg/m^2 is a risk factor for persistent advanced fibrosis; S. Petta et al[21]. also confirmed that a high body mass index causes persistent fibrosis in NAFLD patients eventually leading to irreversible cirrhosis, and there is also a meta-analysis that indicates that a high body mass index in NAFLD index had a higher incidence of advanced fibrosis in the NAFLD population[22]. The above studies demonstrated that a high body mass index predicted the development of advanced liver fibrosis.

Secondly, for serum albumin, it has been shown that human serum albumin is an important plasma protein produced by the liver[23]. There are many recognized clinical indications in chronic liver disease and advanced liver fibrosis is associated with decreased serum albumin, and necrosis and persistent inflammation of hepatocytes reduce albumin synthesis. Albumin internalizes and inhibits TLR signaling in vivo and regulates the immune cell transcriptome, thereby protecting the liver from TNFa-induced immunopathy[24]. Also, the major form of albumin is the reduced state of free sulfhydryl groups present in Cys-34 residues, which is an important source of extracellular antioxidant function, as sulfhydryl groups are potent free radicals for reactive oxygen species (ROS) and reactive nitrogen species (RNS) scavengers, and oxidative stress is the result of ROS and RNS release from innate immune cells, albumin can eliminate oxidative stress by replenishing plasma thiols and antioxidant function[25]. Oxidative stress plays an important role in the pathogenesis of acute-on-chronic liver disease and can lead to liver fibrosis by promoting the activation of hepatic stellate cells[24], [26]. The above studies have shown to some extent that normal serum albumin has a liver with a protective effect, and reduced albumin levels in patients with fibrosis in NAFLD can lead to more severe liver fibrosis in patients.

For platelet count, it has been noted that platelet count tends to decrease linearly with increasing degree of liver fibrosis and is an ideal biomarker to determine the severity of fibrosis in patients with NAFLD[27]. Normal platelets are actively involved in the pathophysiological processes of the liver, and platelets play an important role in liver inflammation by interacting with hepatic sinusoidal endothelial cells and bone marrow cells to induce different hepatic processes that regenerate and repair necrotic inflammation and fibrosis of liver cells, among others[28]. The thrombocytopenia associated with advanced liver tissue fibrosis is thought to be a consequence of hypersplenism, due to enlargement secondary to portal hypertension, which increases platelet aggregation and accelerates platelet destruction in the spleen. Secondly, a decrease in thrombopoietin may also contribute to thrombocytopenia in patients with advanced chronic liver disease, as thrombopoietin is synthesized in the liver and is involved in megakaryocyte growth and platelet production[29-31]. Studies have also found that reduced platelet count is an independent predictor of the severity of fibrosis in cirrhosis, NAFLD[32].

In the case of aspartate aminotransferase, which is found mainly in liver tissue and is closely associated with the presence of liver injury, the increase in liver inflammation with the development of

ISSN 2706-6819 Vol.5, Issue 6: 34-45, DOI: 10.25236/IJFM.2023.050607

liver fibrosis is reflected in increased levels of aspartate aminotransferase. It has been shown that alanyl-glutamine treatment significantly attenuates methionine- and choline-induced liver pathological changes reduces aspartate aminotransferase levels, decreases liver inflammation and collagen deposition in liver fibrosis, promotes recovery from hepatocellular injury, and thus inhibits the progression of liver fibrosis[33, 34]. The above studies have shown to some extent that high levels of aspartate aminotransferase are predictive of liver In addition, meta-analysis showed that aspartate aminotransferase increased with the severity of fibrosis in advanced NAFLD[35].

Long-term hyperlipidemia causes lipid deposition in the vessel wall, leading to endothelial damage and infiltration of inflammatory cells in the vessel wall, and activated inflammatory cells release a series of inflammatory factors such as IL-6 and TNF-α. Damage to the vascular endothelium can also increase the release of TNF-α, thus inducing liver fibrosis[36, 37]. Mansour-Ghanaei F et al[38] showed that hyperlipidemia is a major risk factor for NAFLD and plays an important role in the development of NAFLD. However, there are no definite clinical studies to confirm whether there is a close relationship between hyperlipidemia and the progression of liver fibrosis and whether it leads to the progression of early liver fibrosis to advanced stages. The present meta-analysis was performed to study the progression of liver fibrosis on the basis of NAFLD, and the results showed that hyperlipidemia had no direct effect on the progression of liver fibrosis. There may be contradictions between the existing studies and the available literature, and the reason for this may be the small sample size included in the study.

The number of included studies that we finally used to assess each risk factor by literature search was relatively small, and the relevant literature was obtained from the PubMed database. Also, all articles included in the meta-analysis were case-control and cohort studies, thus potentially subject to errors and limitations. In future studies, the risk factors for liver fibrosis progression should be further confirmed by expanding the sample size and combining clinical studies as much as possible.

5. Conclusion

The main risk factors for the progression from early to advanced stages in patients with NAFLD fibrosis are diabetes, high body mass index, low serum protein, low platelet count, and high levels of aspartate aminotransferase. The results of this study can be used to identify risk factors for progression to advanced stages in patients with NAFLD liver fibrosis in advance of clinical practice and to develop appropriate prevention strategies, thereby reducing the incidence and treatment costs of advanced fibrosis.

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