

# INPLASY PROTOCOL

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## Atherogenic Index of Plasma in Non-Alcoholic Fatty Liver Disease: Systematic Review and Meta- Analysis

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**Review question / Objective:** P - Non-alcoholic fatty liver disease (NAFLD) I - Atherogenic index of plasma (AIP) C - Imaging and histopathology O - Mean difference and Area Under the Curve S - Observational studies.

**Condition being studied:** Non-alcoholic fatty liver disease (NAFLD), is a common liver disease characterized by the presence of excessive fat build up within hepatocytes, in the absence of other conditions that result in hepatic steatosis and with little to no alcohol consumption. It refers to a broad range of conditions including steatosis, non-alcoholic steatohepatitis (NASH) and cirrhosis.

**INPLASY registration number:** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 13 August 2022 and was last updated on 13 August 2022 (registration number INPLASY202280043).

### INTRODUCTION

**Review question / Objective:** P - Non-alcoholic fatty liver disease (NAFLD) I - Atherogenic index of plasma (AIP) C - Imaging and histopathology O - Mean difference and Area Under the Curve S - Observational studies.

**Rationale:** Histopathological evaluation using liver biopsy is the gold standard for evaluating hepatic steatosis and diagnosing NAFLD, however this invasive diagnostic modality comes with its limitations including high cost, sampling errors and post procedure complications. Hence multiple studies investigated several non-invasive modalities for NAFLD diagnosis including potential biomarkers.

Atherogenic index of plasma (AIP), a novel quantitative index utilized to assess lipid levels, is a strong marker of dyslipidemia. AIP has been lately investigated as a potential predictive marker for the detecting NAFLD, with conflicting results. Therefore, we conducted a systematic review and meta-analysis to evaluate AIP levels in NAFLD patients and assess its accuracy in predicting NAFLD. We also assessed the effect of gender on AIP in patients with NAFLD.

**Condition being studied:** Non-alcoholic fatty liver disease (NAFLD), is a common liver disease characterized by the presence of excessive fat build up within hepatocytes, in the absence of other conditions that result in hepatic steatosis and with little to no alcohol consumption. It refers to a broad range of conditions including steatosis, non-alcoholic steatohepatitis (NASH) and cirrhosis.

## METHODS

**Search strategy:** For PubMed, the following search strategy was used: ("Non-alcoholic Fatty Liver Dis-ease"[Mesh]) OR ("Non-alcoholic Fatty Liver Disease"[All Fields]) OR (NASH) OR ("metabolic dysfunction associated fatty liver disease") OR ("metabolic-dysfunction-associated fatty liver disease") OR ("metabolic associated fatty liver disease") OR (MAFLD)) AND ("Atherogenic index of plasma" OR (AIP)), while a similar search was performed for EMBASE and Scopus electronic databases.

**Participant or population:** Non-alcoholic fatty liver disease patients.

**Intervention:** Atherogenic index of plasma (AIP).

**Comparator:** Imaging and histopathology.

**Study designs to be included:** Observational studies.

**Eligibility criteria:** The inclusion criteria for this study compromised observational cohort, case-control, or cross-sectional studies assessing AIP in NAFLD; hepatic

steatosis evaluated through imaging such as ultrasonography or histologically through liver biopsy; human studies without restriction to gender, race, or ethnicity; and studies published in English. Whereas the exclusion criteria were studies including patients with secondary hepatic steatosis due to other causes; conference abstracts or papers, posters, published abstracts without full article, letters, notes, and editorials; studies including patients with the polycystic ovarian syndrome; participants under the age of 18; and interventional studies.

**Information sources:** An electronic search of several databases, including PubMed, EMBASE, and Scopus was carried.

**Main outcome(s):** Mean difference and Area Under the Curve of Atherogenic Index of Plasma (AIP).

**Additional outcome(s):** The effect of sex on AIP levels and AUROC in patients with NAFLD and controls.

**Data management:** The search results' titles and abstracts were analyzed for eligibility, and then the full text was assessed to make sure the inclusion and exclusion criteria were satisfied. The author (O.C.) extracted the data from the included articles, and another verified it (A.I.). Name of the author, year and country of publication, study design, total sample size, population under study, percentage of patients with NAFLD in the sample size, the technique used to diagnose NAFLD, mean age, gender ratio, body mass index (BMI), mean  $\pm$  standard deviation or median of AIP of the sample, and area under the receiver operating characteristic (AUROC) curve were among the data that were extracted.

**Quality assessment / Risk of bias analysis:** The included studies' quality, bias, and internal validity were evaluated using the QUADAS-2 quality assessment tool by two investigators (O.C.) and (M.I.). In case of disagreement between the investigators, a consensus was reached through discussion. Answers for each assessment

category were "yes," "no," or "unclear." The QUADAS-2 assessment had no impact on the studies' eligibility.

**Strategy of data synthesis:** The data collection for the systematic review and the meta-analysis were analyzed in R with the Metafor package in OpenMeta[Analyst]. The association between AIP and NAFLD was assessed using mean difference (MD) and AUC, which examined the accuracy of AIP in predicting NAFLD. The  $\chi^2$ -based Q-test and I<sup>2</sup> were used to assess the heterogeneity between studies. Heterogeneity was categorized using the Cochrane Handbook; I<sup>2</sup> values between 0% and 40% were not important, 30% to 60% to be moderate, 50% to 90% to be substantial, and 75% to 100% to be significant. From studies that reported median and interquartile range (IQR), mean and standard deviation (SD) were calculated. The confidence interval and the point estimate were conducted to identify the AUC's standard error. Statistics were combined in some studies with multiple subgroups to assess the mean and SD for the entire sample size. The Cochrane Handbook's recommendations were followed while doing this. For all the meta-analyses, restricted maximum likelihood random-effects models were used. The included studies' data were analyzed as mean differences with a 95% confidence interval, lower bound, upper bound, standard error, and p-value, or as AUCs with the same set of parameters. Statistical significance was defined as a p-value <0.05. An analysis was performed only when there were at least two studies that reported AIP values with mean and SD or median and IQR, or AUC with upper and lower confidence intervals.

**Subgroup analysis:** Subgroup analysis according to AIP levels and AUROC in different sexes was evaluated.

**Sensitivity analysis:** Not performed.

**Language restriction:** Studies included had to be published in English.

**Country(ies) involved:** Romania, Ireland.

**Keywords:** Non-alcoholic fatty liver disease (NAFLD); metabolic-dysfunction-associated fatty liver disease (MAFLD); hepatic steatosis; liver fibrosis; biomarkers; scores; non-invasive diagnosis.

**Dissemination plans:** Publication in a peer-reviewed journal.

**Contributions of each author:**

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