Does NAFLD Fibrosis Score predict mortality risk among MAFLD patients?: a systematic review and meta-analysis

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ABSTRACT

Background: Metabolic dysfunction-Associated Fatty Liver Disease (MAFLD) is a prevalent liver disease affecting 1 million people and projected to be the leading cause of liver transplantation in 2030 due to its progression of liver fibrosis. Several non-invasive scoring systems have been established to predict advanced fibrosis among MAFLD patients, namely NAFLD Fibrosis Score (NFS). Whether its performance remains useful in determining mortality risk in the MAFLD population is less clear. This study was aimed to assess the usefulness of NFS to predict mortality risk among MAFLD patients.

Method: A systematic search was conducted on Pubmed, ProQuest, and ScienceDirect from inception to February 28, 2021. All studies that met the inclusion criteria investigating MAFLD patients diagnosed with biopsy or non-biopsy were included. Bias risk was assessed using The Newcastle-Ottawa Scale. The outcome was mortality risk. We used a random-effects model, and data were pooled to determine the risk ratio (RR) and its 95% CI. Meta-analysis was conducted using Review Manager 5.3.

Result: 9 cohort studies comprising 21,041 MAFLD patients were included. The risk of bias was found to be low. Pooled analysis showed that high NFS (>0.676) was significantly associated with increased mortality (RR=3.14; 95%CI=2.35-4.19; p<0.00). The finding was more prominent in the biopsy-proven MAFLD subgroup (RR=3.75; 95%CI=2.20-6.38; p<0.00).

Conclusion: High NFS is associated with an increased risk of death in MAFLD patients.

Keywords: NFS, MAFLD, NAFLD, mortality, prognostic.


INTRODUCTION

Metabolic dysfunction-Associated Fatty Liver Disease (MAFLD) is a novel classification proposed for nonalcoholic fatty liver disease (NAFLD).¹ It now accounts for the most prevalent liver disease, affecting almost 1 million people worldwide. This high prevalence and its progressive state to cirrhosis and hepatocellular carcinoma is projected to be the leading cause of liver transplantation by 2030.¹ Prior studies have shown that advanced fibrosis is an independent predictor for liver-related events and all-cause mortality among MAFLD patients.²⁶ However, routine liver biopsy is not achievable in daily clinical practice and population settings, considering the high prevalence, potential complications, and cost. Although MAFLD is a disease that possesses a broad spectrum of clinical course, employing a complex prognostic study will not be feasible. Furthermore, a different spectrum of the disease has different fibrosis as well as mortality risk.

Several non-invasive scoring systems have been developed and validated to detect liver fibrosis in MAFLD patients, such as NAFLD Fibrosis Score (NFS), a combination of age, transaminases, and platelet count-The-Fibrosis 4 (FIB-4) Index, and AST to Platelet Ratio Index (APRI). Along with the FIB-4 index, NFS is the recommended non-invasive tool to predict advanced fibrosis in MAFLD patients.² However, it remains unclear whether NFS's performance can also predict mortality risk in MAFLD populations. This study aims to systematically summarize the current evidence of prognostic usefulness in MAFLD patients.

METHODS

This systematic review and meta-analysis adhered to PRISMA guideline. Two independent investigators conducted a literature search from PubMed, ProQuest, and ScienceDirect from inception to February 28, 2021, restricting the search to studies involving humans and published in English. For the keywords, medical subject headings (Mesh) and free-text phrases which were; (((("Non-alcoholic Fatty Liver Disease"[Mesh]) OR ("non alcoholic fatty liver disease"[All Fields])) OR ("maflD"[All Fields])) OR ("maflD"[All Fields])) OR (""metabolic associated fatty liver disease"[All Fields])) AND ((("Cohort Studies"[Mesh]) OR ("Retrospective Studies"[Mesh])) OR ("cohort"[All Fields]) OR ("retrospective"[All Fields]))) AND ((("Mortality"[Mesh]) OR ("Survival"[Mesh])) OR ("mortality"[All Fields]))) OR ("mortality"[Mesh]) OR ("survival"[Mesh]) OR ("Mortality"[Mesh]) OR (" Survival"[Mesh]) OR ("Mortality"[Mesh]) OR ("Survival"[Mesh]) OR ("mortality"[All Fields])).

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Fields) OR (“survival”[All Fields])) were used in this study. In addition, a manual search was also performed to retrieve potential articles without missing any additional eligible studies.

Studies were included if they met the following criteria: the study was a cohort study; the study group was MAFLD patient; the study estimated the usefulness of high NFS (> 0.676) on mortality risk in MAFLD patients; the outcome was mortality; adjusted risk ratio (RR) with their corresponding 95% confidence intervals (CIs) or raw data to estimate these findings were reported. The risk of bias of included studies was assessed by using the Newcastle-Ottawa Scale (NOS). Studies with NOS scores < 7 were considered to have a high risk of bias, whereas those with a score ≥ 7 a low risk of bias. The excluded literatures were as follows: review/case reports/cross-sectional/case-control studies; general population (non-disease specific populations) as the study group; non-English articles. Research would also be excluded if any desirable data could not be retrieved.

The same two authors used a predefined form to extract the following data from each study: author, publication year, country or area where the research was performed, follow-up length, sample size, events of mortality, MAFLD diagnostic methods, cofounder changes if any, and adjusted/unadjusted RR with their respective 95 percent CIs. Contacts to authors for additional data or clarification were made when needed.

The pooled RR estimated the high NFS’s impact on MAFLD patients’ mortality with their corresponding 95% CI, measured by models based on fixed-effects or random-effects assumptions. Z test of the overall effect was considered to be significant if p-value < 0.05. Heterogeneity was assessed using the I² statistic. Potential publication bias will be evaluated by visual inspection of the funnel plot; an asymmetric plot could suggest possible publication bias. All statistical analyses were performed using Review Manager version 5.4 (The Cochrane Collaboration).

**RESULTS**

Of the 422 potential records initially identified, 399 were discarded after removing duplicates and eligibility screening of titles and abstracts. After further full-text examinations for 23 articles, nine cohort studies investigating the usefulness of high NFS and mortality risk in MAFLD patients were considered eligible for further qualitative and quantitative synthesis (Figure 1).

The baseline characteristic of the nine cohort studies and their corresponding NOS scores were summarized in Table 1. The studies involved 21,041 MAFLD patients, ranging from 153 to 14,841 patients in each study, originating from 10 different countries. Of 9 included studies, three studies took samples of Asian populations, two studies took European populations, while the six studies took samples from Canada and United States. Studies were published between 2013 and 2019. The follow-up duration ranged from 5 to 20 years. Methods of MAFLD diagnosis varied; 5 studies diagnosed MAFLD through liver biopsy, two studies used ultrasonography. The last two studies used negative for the viral markers indicator and the United States Fatty Liver Index (USFLI). As shown in Table 1, the study quality ranged from 7 to 9. All studies were considered at low risk of bias.

The data evaluating high NFS and mortality risk in MAFLD patients were limited. Pooled results on high NFS and risk of mortality were shown in Figure 2a. High NFS was significantly associated with mortality in MAFLD patients (pooled RR, 3.27; 95%CI 2.34-4.56), with substantial heterogeneity among these studies (I² = 89%, p <0.00). Subgroup analysis was further conducted by categorizing studies based on MAFLD diagnosis methods, as shown in Figure 2b. The association was more prominent in the biopsy-proven MAFLD subgroup (RR=3.75; 95%CI=2.20-6.38; p<0.00). No statistically significant subgroup effect was found (p=0.50). Because of the limited number of studies, a funnel plot analysis of publication bias was not possible.

A sensitivity analysis was conducted due to the considerable amount of heterogeneity found. The estimated...
association between high NFS and mortality risk changed slightly while remaining statistically significant after deleting a particular study, which indicated that no single study has an excessive influence on the pooled effect.

### DISCUSSION

The current study examined NFS’s prognostic usefulness, a simple and accessible clinical variable in MAFLD patients. This meta-analysis of 9 observational studies showed that high NFS (> 0.676) was significantly correlated with an almost fourfold higher risk of mortality in MAFLD patients compared to Low-Intermediate NFS (≤ 0.676). The association was more elevated in the biopsy-proven MAFLD subgroup than that of non-biopsy-proven MAFLD. Significant heterogeneity was detected, although no significant change was found in the sensitivity analysis.

In the regular clinical setting, recognizing a subgroup of MAFLD patients at risk of mortality is essential. The finding of liver fibrosis in liver biopsy has long been an independent predictor of poor outcome and mortality in MAFLD patients. However, its serial use for prognostication deems to be impractical due to the possibility of side-

### Table 1. Characteristics of included studies

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Country</th>
<th>Follow-up duration</th>
<th>Sample size/Events of Mortality</th>
<th>Methods of MAFLD diagnosis</th>
<th>Adjusting for confounding factors</th>
<th>NOS Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angulo, 2013⁵</td>
<td>Multicenter (5 countries)</td>
<td>104.8 months (median)</td>
<td>320/41</td>
<td>Biopsy</td>
<td>Sex, presence of hypertension, race, statin use, and stage of fibrosis</td>
<td>8</td>
</tr>
<tr>
<td>Trepersertsuk, 2013⁹</td>
<td>United States</td>
<td>12±3.9 years (mean)</td>
<td>302/39</td>
<td>Biopsy</td>
<td>None</td>
<td>7</td>
</tr>
<tr>
<td>Xun, 2014¹⁰</td>
<td>China</td>
<td>6.6 years (median)</td>
<td>180/12</td>
<td>Ultrasonography</td>
<td>None</td>
<td>7</td>
</tr>
<tr>
<td>Sebastiani, 2015³</td>
<td>Canada</td>
<td>5 years (median)</td>
<td>148/11</td>
<td>Biopsy</td>
<td>Sex</td>
<td>9</td>
</tr>
<tr>
<td>Unalp-Arida, 2017¹¹</td>
<td>United States</td>
<td>19.3 years (median)</td>
<td>14,841/4,835</td>
<td>Negative for viral markers</td>
<td>Several demographic and clinical variables</td>
<td>7</td>
</tr>
<tr>
<td>Le, 2017¹²</td>
<td>United States</td>
<td>20 years</td>
<td>1,936/NA</td>
<td>USFLI</td>
<td>None</td>
<td>8</td>
</tr>
<tr>
<td>Peleg, 2018¹³</td>
<td>Israel</td>
<td>100.23 months (mean)</td>
<td>153/19</td>
<td>Biopsy</td>
<td>None</td>
<td>7</td>
</tr>
<tr>
<td>Golabi, 2018¹⁴</td>
<td>United States</td>
<td>207 months (median)</td>
<td>2,515/754</td>
<td>Ultrasonography</td>
<td>Several demographic and clinical variables</td>
<td>7</td>
</tr>
<tr>
<td>Hagstorm, 2019¹⁵</td>
<td>Sweden</td>
<td>19.9±8.7 years (mean)</td>
<td>646/214</td>
<td>Biopsy</td>
<td>Age, sex, T2DM, hypertension, and BMI</td>
<td>8</td>
</tr>
</tbody>
</table>

NA=not available; T2DM=type 2 diabetes mellitus; BMI=body mass index.
effects, measurement errors, and high cost.\textsuperscript{5,16} Other non-invasive tools that have been widely studied and validated for determining liver fibrosis are imaging-based studies. A prior meta-analysis conducted by Xiao found that imaging-based studies such as FibroScan and other types of elastography; shear wave elastography, and magnetic resonance elastography yielded the best diagnostic performance for liver fibrosis among other non-invasive tools.\textsuperscript{17} Although there are only a handful of longitudinal studies examining the association of elastography or imaging-based examinations with risk of death among MAFLD population, in contrast with the studies relating to liver fibrosis.\textsuperscript{18-20} While early evidence shows promising results, imaging-based studies’ low availability is what makes it impossible to employ these techniques in daily clinical settings, mostly in primary care. Thus, the goal of early identification of subgroups who are at higher risk will not be achieved. By contrast, non-invasive scores are widely available. They are mainly composed of readily available demographic and clinical variables, as well as simple blood tests.

NFS is one of the established non-invasive scores, consisting of simple demographic and clinical variables, such as age and BMI, and laboratory parameters, such as plasma glucose, transaminases, platelet count, and albumin.\textsuperscript{21} Its performance to determine liver fibrosis has been established. However, the usefulness of NFS to predict mortality risk in MAFLD patients is less well-known. This study presented strong evidence correlating NFS with mortality risk among MAFLD patients, as previously mentioned. Even in comparison with other non-invasive scores, as mentioned in studies by Angulo and by Xun, NFS presents evidence as a superior tool to predict mortality, compared with the FIB-4 index and APRI.\textsuperscript{5,10}

This study had some limitations. First, substantial heterogeneity was found. This might be due to differences in patients enrolled and diagnosis method of MAFLD in each study. Two studies used ultrasonography, and one study used negative for viral markers to diagnose MAFLD, which could contribute to a much lower diagnostic accuracy, as opposed to liver biopsy. Second, there were only limited studies to date, hence assessing publication bias due to the high amount of positive studies was not feasible. Third, conducting a side-by-side analysis of non-invasive scores would present more solid evidence of NFS’s usefulness in predicting mortality risk; however, so far, only two available studies have done so. Thus, comparison analysis could not be conducted.

**CONCLUSION**

This meta-analysis provided evidence that high NFS, a simple and readily available tool, is associated with an increased risk of death in MAFLD patients. Findings also show that high NFS may be considered to be used as a non-invasive option other than biopsy.

**DISCLOSURE**

**Statement of Ethics**

There are no human participants in this research. Thus, there was no need for ethical approval.

**Conflict of Interest**

The authors declare no conflict of interest related to the material presented in the study.

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The authors received no external funding.

**Author contributions**

Both Adinda Rahadini and Adinda Rahadina designed the concept of the study, did literature search, extracted data, as well as wrote the original manuscript. Adinda Rahadini conducted all data and statistical analyses. All authors approved the final version of the manuscript.

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