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Review Article

Association of Cardiovascular Disease to Non-Alcoholic Fatty Liver Disease: A Call for Awareness Among Physicians

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ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) has become the most common liver disease worldwide. Patients with NAFLD remain at a higher risk of extrahepatic co-morbidities including cardiovascular disease (CVD). Several long term follow up studies have shown that CVD related mortality is the most common cause of mortality in patients with NAFLD without cirrhosis. The association of NAFLD to CVD remains independent despite common metabolic risk factors like obesity, dyslipidaemia, diabetes and hypertension. In the current review article, we discuss association of CVD to NAFLD and its implications in Indian population.

Keywords: Cardiovascular Disease; CVD Risk Factor, Metabolic Risk Factor; Non-Alcoholic Fatty Liver Disease.

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) encompasses non-alcoholic fatty liver (NAFL) or simple steatosis, non-alcoholic steatohepatitis (NASH), cirrhosis and hepatocellular carcinoma.[1,2] NAFLD is gradually increasing as a cause of liver disease and cirrhosis.[3] NAFLD is also associated with extrahepatic diseases that include cardiovascular disease (CVD), chronic kidney disease and malignancies. CVD and NAFLD generally share common risk factors like obesity, dyslipidaemia, diabetes mellitus (DM) and hypertension, however, multiple studies have shown that NAFLD is also independently associated with CVD despite presence of confounders (metabolic risk factors).[4]

CVD has been shown to be the most common cause of death in patients with NAFLD and this risk is more in patients with NASH as compared to simple steatosis or non-alcoholic fatty liver (NAFL).[5-8]

Majority (not all) of these studies have shown that risk of cardiovascular events/mortality is more in these patients as compared to controls.[4-9] We discuss association of CVD with NAFLD and its implications for India in the current review.

PREVALENCE OF NAFLD IN INDIA

NAFLD is the most common liver disease worldwide and in India. The Indian studies on prevalence of NAFLD are shown in table 1.[10-19] Some observations are noteworthy.

The prevalence of NAFLD in urban India ranges from 16% to 53%.[10-13] There is less data from rural India, and in pediatric/a adolescents age group. One rural study from west Bengal showed prevalence of 8.7%, the other rural study from Haryana showed NAFLD prevalence as 30.4%.[14,15] These 2 studies had quite different body mass index (BMI), 19.6 ±6.6 in west Bengal study and 25.2±4.8 in Haryana study, that probably explains difference of prevalence in NAFLD and suggests that rural NAFLD is also significant problem. Jain et al analyzed data of 218 overweight individuals, aged 10-16 years. The authors noted 62.5% prevalence of NAFLD.[16]

Das et al analyzed data of 961 school children, aged 5-10 years from Faridabad, Haryana. The authors noted 22.4% prevalence of NAFLD.[17] Three studies have looked at prevalence fo NAFLD in type 2 diabetes mellitus (T2DM). Mohan et al showed a prevalence of 54.5% among diabetic subset of study population.[12] Kalra et al analyzed 924 patients, aged 25-84 years, enrolled at 189 centers from 101 cities in India. A total of 56.5% had NAFLD.[18] Vanjiappan et al reported 61% prevalence of NAFLD in a study including 300 patients with T2DM.[19] All these studies have used imaging hat may miss mild steatosis, thus actual prevalence of NAFLD should be higher. A liver biopsy and magnetic resonance-based fat fraction are better to make a diagnosis, as these modalities can pick up mild steatosis also.[20,21]

Table 1: Epidemiology of NAFLD in India

Author[ref.] (year)	n	NAFLD	Study population, place of study, rural/urban
Singh,[10] 2004	159	24.5%	Odisha
Amarapurkar,[11] 2007	1168	16.4%, 18.9% in >20 years	Mumbai
Mohan,[12] 2009	541	32% overall, 54.5% in diabetics	Chennai
Najmy[13], 2019	986	53.5%	Chandigarh
Das[14], 2010	1911	NAFL 8.7%, NAFL with elevated ALT 2.3%, cirrhosis 0.2%	West Bengal, rural population, BMI 19.6 ±6.6
Majumdar[15], 2016	176	30.4%	Rural Haryana, 25.2±4.8 versus 21.4±4.3 in normal, > 35 yr of age included
Jain[16], 2018	218, age 10-16 years	62.5%	Overweight adolescents, New Delhi
Das[17], 2017	961 school children, 5-10 years age	22.4% total, 18.9% in normal-weight and 45.6% overweight	Urban, Faridabad, Haryana
Kalra[18], 2013	924	56.5%	Diabetic population, multicenter study
Vanjiappan[19], 2018	300	61%	Diabetics, associated with cardiovascular risk factors, Puducherry

However, these modalities cannot be used in community setting due risk of complications (biopsy) and unavailability (MR fat fraction). A study from apparently healthy living liver donors, where liver biopsy was done before donation, showed a 50.4% prevalence of NAFLD.[20] Thus, NAFLD is very common in India.

INDIANS ARE AT MORE RISK OF CVD

Indians have CVD at an early age as compared to Western population.[22,23] The Interheart study, which was conducted across 52 countries included 15152 cases and 14820 controls. The south Asians were 10 years younger at first presentation of acute myocardial infarction, and also had higher proportion of cases with ≤40 years.[22] Gupta et al studied CVD risk factors across various age groups in urban Indians. The authors found a rapid escalation of CVD risk factors in 30-39 years age group.[24] Indian are predisposed to metabolic risk factors at a lower body mass index (BMI) and the cut offs for defining overweight and obesity are lower as compared to Western population.[25] As NAFLD independently adds to risk of CVD, it should be part of risk scores for better CVD risk assessment in general population, however data is limited at present. It has been suggested that patients with low risk by risk-scores should be managed with life style modification that should improve their CVD risk also. Patients with intermediate or high risk by risk-scores should be referred to a cardiologist for evaluation of CVD. [26]

WHY NAFLD IS INDEPENDENTLY ASSOCIATED WITH CVD?

CVD and NAFLD are associated with some common metabolic risk factors like diabetes, dyslipidaemia, hypertension and obesity. Still, several potential links make NAFLD important and independent risk factor pathogenesis of CVD. These possible links which may cause atherosclerosis acceleration include genetics, atherogenic dyslipidaemia, chronic inflammation and imbalance of pro and anticoagulant factors. In addition to NAFLD, insulin resistance, oxidative stress and adiponectin imbalance also contribute to CVD.[4,27-34] Atherogenic dyslipidaemia, characterized by high triglycerides and low high-density lipoprotein is frequently present in NAFLD. NAFLD is associated with small dense and oxidized low-density lipoprotein (LDL) which are more atherogenic. DeFilippis et al, compared 569 patients with NAFLD to 2793 non-NAFLD. The authors showed that NAFLD was independently associated with higher triglycerides and lower HDL.[29] In addition, patients with NAFLD had higher LDL particle concentration with lower particle size and the lipoprotein abnormalities in NAFLD were associated with severity of hepatic steatosis.[29] In another study, these lipid abnormalities occurred more commonly in patients NASH in comparison to NAFL.[30] The inflammatory markers are increased in patients with accelerated atherosclerosis,[33] which is consistent with high-sensitivity C-reactive protein (hs-CRP) in NAFLD, representing sub-clinical inflammation. Nigam et al showed that increase of hs-CRP level by 1 mg/dl was associated with 1.7 times higher when compared to controls.[30] NAFLD is associated with TNF-α which causes insulin resistance, leading to lipolysis. These proinflammatory cytokines may also cause endothelial dysfunction.[31-33] Adiponectin works as insulin sensitizer, anti-atherosclerotic and anti-inflammatory agent. NAFLD is associated with low adiponectin which is associated with more extensive necroinflammation.[31,32] Tripodi et al showed that patients with NAFLD had a procoagulant imbalance that increases from the less severe (steatosis) to more severe (NASH and cirrhosis) forms of the disease. This imbalance was caused by increased factor VIII and reduced protein C. This imbalance may also play a role in the causation of CVD in patients with NAFLD.[35]

CARDIOVASCULAR OUTCOMES IN NAFLD

Several cohorts have shown results of long term follow in patients with NAFLD.[6-9,36-39] Majority (but not all) of studies have shown higher risk of CVD events and CVD related mortality in patients with NAFLD. Ekstedt et al followed up 129 patients with NAFLD,

the mean follow-up was 13.7 years, the most common cause of mortality was CVD followed by malignancies and liver related causes. The increased mortality was present in patients with NASH, not in steatosis only patients.[6] In a study of 256 subjects, aged 45 +/- 12 years, followed up for 21+/- 7.7 years. The CVD related mortality was the most common cause of mortality, risk being more in patients with NASH.[8] Targher et al analyzed data of 2103 (1417 with NAFLD) subjects with a follow up of 6.5 years. The presence of NAFLD was independently associated with fatal and non-fatal CVD events (adjusted HR 1.87).[36] Haring et al analyzed data of 4160 (1249 with NAFLD) subjects. Although the presence of NAFLD was not independently associated with CVD mortality, presence of NAFLD with elevated serum GGT levels were associated with increased risk of CVD mortality in men (adjusted HR 2.41).[7] While most of data regarding NAFLD and CVD is available for CAD, several studies have shown higher risk of stroke in NAFLD.40-43 NAFLD was related to increased risk of CVA (OR = 2.32, 95% CI 1.84-2.93, P < 0.001). The increased risk was seen in both case-control studies (OR = 2.73) and cohort studies (OR = 2.22), respectively. NAFLD was shown to correlate with both cerebral hemorrhage (OR = 1.8) and ischemic stroke (OR = 2.51).[43]

Results of different studies are affected by age of study population as individuals with higher age are at more risk for CVD, race and presence of other metabolic risk factors. Table 2 shows meta-analysis regarding risk risk of CVD in patients with NAFLD.[44-46] Wu et al included 34 studies (21 cross-sectional studies, and 13 cohort studies) comprising of 164,494 participants in a recent meta-analysis. The authors showed that NAFLD was associated with higher incident (HR=1.37) and prevalent (OR=1.81) CVD, but not with higher mortality.[45] NAFLD was associated with increased risk of prevalent [odds ratio (OR) 1.87] and incident (HR=2.31) coronary artery disease (CAD), hypertension and prevalent atherosclerosis (OR = 1.32).[45]

Kapuria et al included 12 studies in a meta-analysis that used coronary artery calcium as a marker for atherosclerosis. The meta-analysis included a total 42410 subjects including 16883 patients with NAFLD. The mean coronary artery calcium score was significantly higher in NAFLD (OR 1.64, 95% confidence interval 1.42-1.89). This association remained significant in subgroup analyses also for studies with >1,000 subjects and a coronary artery calcium score cutoff of >100.[46] Targher et al included 16 studies with 34,043 adult individuals (36.3% had NAFLD). There were approximately 2,600 CVD outcomes (>70% CVD deaths) during a median follow up of 6.9 years. Patients with NAFLD had a higher risk of both fatal and non-fatal CVD events (OR 1.64, 95% CI 1.26–2.13). This risk was higher in patients with severe NAFLD (OR 2.58; 95% CI 1.78–3.75).[46]

Table 2: Studies of Association between CVD and NAFLD

Author (year)	n	Results	Comments
Wu[44], 2016	Thirty-four studies (164,494 participants, 21 cross-sectional studies, and 13 cohort studies)	NAFLD was not associated with overall mortality (HR = 1.14) and CVD mortality (HR = 1.10). NAFLD was associated with an increased risk of prevalent (OR = 1.81) and incident (HR = 1.37) CVD. Increased risk of prevalent (OR = 1.87) and incident (HR = 2.31) coronary artery disease	presence of NAFLD is associated with an increased risk of major adverse CVD events, although it is not related to mortality
Kapuria[45], 2018	12 studies, 42,410 subjects were assessed, including 16,883 patients with NAFLD	Mean coronary artery calcium score was significantly higher in subjects with NAFLD compared to those without NAFLD (odds ratio 1.64).	Higher aspartate aminotransferase levels were also associated with increased subclinical atherosclero sis (mean difference 1.77; 95% confidence interval, 1.19-2.34)
Targher[46], 2016	16 observational prospective and retrospective studies with 34,043 adult individuals (36.3% with NAFLD) and approximately 2,600 CVD outcomes (>70% CVD deaths) over a median period of 6.9years	Patients with NAFLD had a higher risk of fatal and/or non-fatal CVD events than those without NAFLD (odds ratio [OR] 1.64)	Patients with more 'severe' NAFLD were also more likely to develop fatal and non-fatal CVD events (OR 2.58; 1.78-3.75)

CONCERN REGARDING ASSOCIATION OF CVD AND NAFLD

As both CVD and NAFLD develop slowly over many years, primary prevention is possible. The treatment of NAFLD include life style modification; by exercise, dietary modification and weight loss along with pharmacotherapy in present of NASH. This treatment also improves CVD risk profile. A diagnosis of NAFLD which is incidentally picked up by ultrasound abdomen or raised liver enzymes generally, provides an opportunity to prevent both liver related and CVD related morbidity or mortality. Most of these patients came to primary care physicians first. There is no data related to awareness of physicians regarding NAFLD, and association of NAFLD with CVD from India. Several studies are

available from western world, which show significant lack of awareness. Said et al analyzed results of a survey among 250 primary care physicians. Eighty five percent of physicians underestimated the prevalence of NAFLD. Although majority were aware that NAFLD is associated with metabolic risk factors, only 46% screened diabetic obese patients for NAFLD. Only 8% of physicians would recommend Vitamin E for treatment of NAFLD.[47] A national online survey from USA included 152 primary care physicians, and 150 specialists (gastroenterologists and hepatologists). Forty-nine percent of the primary care physicians chose either not familiar or unaware of differences while 88 % specialists were extremely or very familiar with the differences between NAFLD and NASH. 58 % of those primary care physicians were treating patients with non-alcoholic fatty liver disease and/or non-alcoholic steatohepatitis.[48] Bergqvist et al surveyed 100 clinicians. Seventy five percent believed that the prevalence of NAFLD in the general population is ≤ 10%. Seventy-one percent make no referrals to hepatology for suspected NAFLD. Although 74% agreed liver enzymes are not useful to make a diagnosis of NASH, yet 67% supported 6-monthly liver function tests as a way to monitor progression of NAFLD.[49] Ghevariya et al conducted a survey of 5000 non-institutionalized residents of Brooklyn, USA.[50] The survey questionnaire included awareness of fatty liver, predisposing factors, awareness of cirrhosis, awareness of prevention, diagnostic methods and treatment, and education of physicians to their patients. The majority of subjects were aware of NAFLD and their physicians did not have a discussion about NAFLD. Seventy percent of the study subjects believed that NAFLD is hereditary, only 2% recognized NAFLD as a preventable condition. Ninety-six percent were unaware of the reversibility in early stages of disease and only 5% thought that NAFLD can occur in a non-alcoholic. Ninety-three percent of the subjects were not sure how this condition is diagnosed. Ninety-five percent did not feel that fat deposition in the liver could cause serious health problems.[50]

WHOM TO SCREEN

Kim et al analyzed 11154 participants, from The United States National Health and Nutrition Examination Survey conducted in 1988-1994; with a mean follow up of 14.5 years. NAFLD was diagnosed by ultrasonography and NAFLD fibrosis score; the AST-platelet ratio index and the FIB-4 score were used as indirect markers of liver fibrosis. The mortality in follow up period was not higher for simple steatosis but it increased with increase in fibrosis and was mainly due to cardiovascular causes.[51] Ekstedt et al also showed that liver fibrosis is predictor of mortality, mainly due to cardiovascular causes.[52] It is suggested that NAFLD should also be considered a risk factor for coronary artery disease in patients being evaluated for liver transplantaion.[26] Whom to screen in patients with NAFLD without cirrhosis is not clear at present. The current guidelines from Indian National Association for the Study of the Liver states that CVD evaluation is suggested selectively; in patients with old age or with having metabolic risk factors. A detailed cardiovascular evaluation is recommended in NASH related cirrhosis or hepatocellular carcinoma before liver transplantation.[2] Initially, it was though that NAFL does not progress to fibrosis, however, recent data shows that NAFL also progresses to NASH/fibrosis, although at a slower rate of progression of fibrosis as compared to patients with NASH.[53,54]

CONCLUSIONS

The association of CVD and NAFLD is a matter of concern in Indian setting due to unawareness at primary physician level. As NAFLD is very common among Indian population and development of cirrhosis and CVD takes many years; identification and timely treatment offers a huge opportunity to prevent future liver related and CVD related morbidity and mortality.

REFERENCES

1. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. Hepatology. 2018;67:328-357

2. Duseja A, Singh SP, Saraswat VA, et al. Non-alcoholic fatty liver disease and metabolic syndrome-position paper of the Indian National Association for the study of the liver, endocrine society of India, Indian college of cardiology and Indian society of gastroenterology. J Clin Exp Hepatol. 2015;5:51–68

3. Doycheva I, Issa D, Watt KD, et al. Nonalcoholic Steatohepatitis is the Most Rapidly Increasing Indication for Liver Transplantation in Young Adults in the United States. J Clin Gastroenterol. 2018;52:339-346

4. Fargion S, Porzio M, and Fracanzani AL. Nonalcoholic fatty liver disease and vascular disease: State-of-the-art. World J Gastroenterol. 2014;20: 13306–13324

5. Targher G, Bertolini L, Poli F, et al. Nonalcoholic fatty liver disease and risk of future cardiovascular events among type 2 diabetic patients. Diabetes. 2005;54:3541–3546

6. Ekstedt M, Franzén LE, Mathiesen UL, et al. Long-term follow-up of patients with NAFLD and elevated liver enzymes. Hepatology. 2006;44:865–873

7. Haring R, Wallaschofski H, Nauck M, Dörr M, Baumeister SE, Völzke H. Ultrasonographic hepatic steatosis increases prediction of mortality risk from elevated serum gamma-glutamyl transpeptidase levels. Hepatology. 2009;50:1403–1411

8. Söderberg C, Stål P, Askling J, Glaumann H, Lindberg G, Marmur J, Hultcrantz R. Decreased survival of subjects with elevated liver function tests during a 28-year follow-up. Hepatology. 2010;51:595–602

9. Lazo M, Hernaez R, Bonekamp S, et al. Non-alcoholic fatty liver disease and mortality among US adults: prospective cohort study. BMJ. 2011;343:d6891

10. Singh SP, Nayak S, Swain M, et al. Prevalence of nonalcoholic fatty liver disease in coastal eastern India: a preliminary ultrasonographic survey. Indian J Gastroenterol. 2004;25:76–79

11. Amarapurkar D, Kamani P, Patel N, et al. Prevalence of non-alcoholic fatty liver disease: population-based study. Ann Hepatol. 2007;6:161–163.

12. Mohan V, Farooq S, Deepa M, Ravikumar R, Pitchumoni CS. Prevalence of non-alcoholic fatty liver disease in urban south Indians in relation to different grades of glucose intolerance and metabolic syndrome. Diabetes Res Clin Pract. 2009;84:84–91

13. Najmy S, Duseja A, Pal A et al. Redefining the Normal Values of Serum Aminotransferases in Healthy Indian Males. J Clin Exp Hepatol 2018; In press, DOI: doi.org/10.1016/j.jceh.2018.06.003

14. Das K, Das K, Mukherjee PS, et al. Nonobese population in a developing country has a high prevalence of nonalcoholic fatty liver and significant liver disease. Hepatology. 2010;51:1593–602.

15. Majumdar A, Misra P, Sharma S, Kant S, Krishnan A, Pandav CS. Prevalence of nonalcoholic fatty liver disease in an adult population in a rural community of Haryana, India. Indian J Public Health. 2016;60:26-33
16. Jain V, Jana M, Upadhyay B, Ahmad N, Jain O, Upadhyay AD, Ramakrishnan L, Vikram NK.Prevalence, clinical & biochemical correlates of non-alcoholic fatty liver disease in overweight adolescents. Indian J Med Res. 2018;148:291-301
17. Das MK, Bhatia V, Sibal A, Gupta A, Gopalan S, Sardana R, Sahni R, Roy A, Arora NK. Prevalence of Nonalcoholic Fatty Liver Disease in Normal-weight and Overweight Preadolescent Children in Haryana, India. Indian Pediatr. 2017;54:1012-1016
18. Kalra S, Vithalani M, Gulati G, Kulkarni CM, Kadam Y, Pallivathukkal J, Das B, Sahay R, Modi KD. J Assoc Physicians India. Study of prevalence of nonalcoholic fatty liver disease (NAFLD) in type 2 diabetes patients in India (SPRINT). 2013;61:448-53
19. Vanjiappan S, Hamide A, Ananthakrishnan R, Periyasamy SG, Mehalingam V. Nonalcoholic fatty liver disease in patients with type 2 diabetes mellitus and its association with cardiovascular disease. Diabetes Metab Syndr. 2018;12:479-482
20. Choudhary NS, Saraf N, Saigal S, Gautam D, Lipi L, Soin AS. Estimation of normal values of serum transaminases based on liver histology in healthy Asian Indians. J Gastroenterol Hepatol. 2015;30:763–766
21. Krishan S, Jain D, Bathina Y et al. Non-invasive quantification of hepatic steatosis in living, related liver donors using dual-echo Dixon imaging and single-voxel proton spectroscopy. Clin Radiol. 2016;71:58-63
22. Yusuf S, Hawken S, Ounpuu S, et al; INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet. 2004;364(9438):937-52.
23. Joshi P, Islam S, Pais P, et al. Risk factors for early myocardial infarction in South Asians compared with individuals in other countries. JAMA. 2007;297:286-94.
24. Gupta R, Misra A, Vikram NK, Kondal D, Gupta SS, Agrawal A, Pandey RM. Younger age of escalation of cardiovascular risk factors in Asian Indian subjects. BMC Cardiovasc Disord. 2009;9:28
25. Misra A, Chowbey P, Makkar BM, et al. Consensus statement for diagnosis of obesity, abdominal obesity and the metabolic syndrome for Asian Indians and recommendations for physical activity, medical and surgical management. J Assoc Physicians India. 2009;57:163–170
26. Choudhary NS, Duseja A. Screening of cardiovascular disease in nonalcoholic fatty liver disease. J Clin Exp Hepatol, 2019, accepted, DOI: https://doi.org/10.1016/j.jceh.2019.02.005
27. Kahali B, Liu YL, Daly AK, et al. TM6SF2: catch-22 in the fight against nonalcoholic fatty liver disease and cardiovascular disease?. Gastroenterology. 2015;148:679–684
28. Alkhouri N, Tamimi TA, Yerian L, Lopez R, Zein NN, Feldstein AE. The inflamed liver and atherosclerosis: a link between histologic severity of nonalcoholic fatty liver disease and increased cardiovascular risk. Dig Dis Sci. 2010;55:2644–2650
29. DeFilippis AP, Blaha MJ, Martin SS, et al. Nonalcoholic fatty liver disease and serum lipoproteins: the Multi-Ethnic Study of Atherosclerosis. Atherosclerosis. 2013;227:429–436
30. Nigam P, Bhatt SP, Misra A, Vaidya M, Dasgupta J, Chadha DS. Non-alcoholic fatty liver disease is closely associated with sub-clinical inflammation: a case-control study on Asian Indians in North India. PLoS One. 2013;8:e49286.
31. Hui JM, Hodge A, Farrell GC, Kench JG, Kriketos A, George J. Beyond insulin resistance in NASH: TNF-alpha or adiponectin? Hepatology. 2004;40:46–54
32. Sinn DH, Cho SJ, Gu S, Seong D, Kang D, Kim H et al. Persistent Nonalcoholic Fatty Liver Disease Increases Risk for Carotid Atherosclerosis. Gastroenterology. 2016;151:481–488.e1
33. Matsuzawa Y, Funahashi T, Kihara S, Shimomura I. Adiponectin and metabolic syndrome. Arterioscler Thromb Vasc Biol. 2004;24:29–33
34. Targher G, Day CP, Bonora E. Risk of cardiovascular disease in patients with nonalcoholic fatty liver disease. N Engl J Med. 2010;363:1341–50.
35. Tripodi A, Fracanzani AL, Primignani M, et al. Procoagulant imbalance in patients with non-alcoholic fatty liver disease. J Hepatol. 2014;61:148–154
36. Targher G, Bertolini L, Rodella S, et al. Non-alcoholic fatty liver disease is independently associated with an increased incidence of cardiovascular events in type 2 diabetic patients. Diabetes Care 2007;30:2119–2121
37. Adams LA, Harmsen S, St Sauver JL, et al. Non-alcoholic fatty liver disease increases risk of death among patients with diabetes: a community-based cohort study. Am J Gastroenterol 2010;105:1567–1573.
38. Hamaguchi M, Kojima T, Takeda N, Nagata C, Takeda J, Sarui H et al. Nonalcoholic fatty liver disease is a novel predictor of cardiovascular disease.WorldJ Gastroenterol.2007;13:1579–84.
39. Jepsen P, Vilstrup H, Mellemkjaer L, et al. Prognosis of patients with a diagnosis of fatty liver—a registry-based cohort study. Hepatogastroenterology 2003;50:2101–2104
40. Li H, Hu B, Wei L, Zhou L, Zhang L, Lin Y, Qin B, Dai Y, Lu Z. Non-alcoholic fatty liver disease is associated with stroke severity and progression of brainstem infarctions. Eur J Neurol. 2018 Mar; 25(3):577-e34.
41. Alkagiet S, Papagiannis A, Tziomalos K. Associations between nonalcoholic fatty liver disease and ischemic stroke. World J Hepatol. 2018;10:474-478
42. Bots ML, Salonen JT, Elwood PC, Nikitin Y, Freire de Concalves A, Inzitari D, Sivenius J, Trichopoulou A, Tuomilehto J, Koudstaal PJ, et al. Gamma-glutamyltransferase and risk of stroke: the EUROSTROKE project. J Epidemiol Community Health. 2002;56 Suppl 1:i25–i29
43. Hu J, Xu Y, He Z, Zhang H, Lian X, Zhu T, Liang C, Li J. Increased risk of cerebrovascular accident related to non-alcoholic fatty liver disease: a meta-analysis. Oncotarget. 2017;9:2752–60.
44. Wu S, Wu F, Ding Y, Hou J, Bi J, Zhang Z. Association of non-alcoholic fatty liver disease with major adverse cardiovascular events: A systematic review and meta-analysis. Sci Rep. 2016;6:33386
45. Kapuria D, Takyar VK, Etzion O, Sorana P, O'keffe JH, Koh C. Association of Hepatic Steatosis With Subclinical Atherosclerosis: Systematic Review and Meta-Analysis. Hepatol Commun. 2018;2: 873–83.
46. Targher G, Byrne CD, Lonardo A, Zoppini G, Barbui C. Non-alcoholic fatty liver disease and risk of incident cardiovascular disease: A meta-analysis. J Hepatol. 2016;65:589-600

47. Said A, Gagovic V, Malecki K, Givens ML, Nieto FJ. Primary care practitioners survey of non-alcoholic fatty liver disease. Ann Hepatol 2013;12:758–765
48. Polanco-Briceno S, Glass D, Stuntz M, Caze A. Awareness of nonalcoholic steatohepatitis and associated practice patterns of primary care physicians and specialists. BMC Res Notes. 2016; 9: 157.
49. Bergqvist C-J, Skoien R, Horsfall L, Clouston AD, Jonsson JR, Powell EE. Awareness and opinions of non-alcoholic fatty liver disease by hospital specialists. Intern Med J 2013;43:247–253
50. Ghevariya V, Sandar N, Patel K et al. Knowing What's Out There: Awareness of Non-Alcoholic Fatty Liver Disease. Front Med (Lausanne). 2014; 1: 4
51. Kim D, Kim WR, Kim HJ, Therneau TM. Association between noninvasive fibrosis markers and mortality among adults with nonalcoholic fatty liver disease in the United States. Hepatology. 2013;57:1357–65.
52. Ekstedt M, Hagström H, Nasr P et al. Fibrosis stage is the strongest predictor for disease-specific mortality in NAFLD after up to 33 years of follow-up. Hepatology 2015;61:1547–54.
53. McPherson S, Hardy T, Henderson E, Burt AD, Day CP, Anstee QM. Evidence of NAFLD progression from steatosis to fibrosing-steatohepatitis using paired biopsies: implications for prognosis and clinical management. J Hepatol 2015;62:1148–55
54. Singh S, Allen AM, Wang Z, Prokop LJ, Murad MH, Loomba R. Fibrosis progression in nonalcoholic fatty liver vs nonalcoholic steatohepatitis: a systematic review and meta-analysis of paired-biopsy studies. Clin Gastroenterol Hepatol 2015;13:643–654.

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