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METABOLIC DYSFUNCTION-ASSOCIATED FATTY LIVER DISEASE IN THE ELDERLY PEOPLE

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Resume
Background. As the global population ages, metabolic disorders are becoming increasingly prevalent, leading to a significant rise in fatty liver disease among the elderly. Metabolic-associated fatty liver disease, formerly known as non-alcoholic fatty liver disease, is now the most common liver disease. Closely linked to metabolic disorders like obesity, type 2 diabetes, and dyslipidemia, Metabolic-associated fatty liver disease currently affects 24% of the adult population, equating to one billion individuals worldwide.
Purpose of study. To analyze the incidence structure of metabolically associated fatty liver disease in the elderly population and to determine the mechanisms of liver aging that affect the prevalence and mortality from this disease in an elderly cohort of individuals.
Material and methods of study. For this literature review, we analyzed 32 scientific publications, including reviews, original articles, and meta-analyses, published between 2012 and 2024. We conducted a literature search using databases such as Google Scholar, Web of Science, PubMed, Scopus, and Abridged Index Medicus.
Results. Reviewing the available literature sources has revealed the prevalence of fatty liver disease peaking at the age of 40–50 in men and 60–69 in women but decreasing in the older cohorts (>75 years). The mechanisms of liver cell aging influence the course of this disease in old patients have been identified as well. However, there are no data indicated concerning the direct impact on prevalence and association with fibrosis in the elderly population.
Conclusion. Conflicting data on the prevalence of metabolic-associated fatty liver disease among the diagnosed elderly patients highlight the need for further research to realise the mechanisms underlying the age-related changes in the liver. The study of this disease in elderly persons is rather important to improve the quality of life and optimising medical care and developing prevention and treatment strategies.
Keywords: Non-alcoholic Fatty Liver Disease, Metabolic Dysfunction-Associated Steatotic Liver Disease, Fatty Liver Disease, Old Age, Aging, Prevalence

ЕГДЕ ЖАСТАҒЫ АДАМДАРДА БАУЫРДЫҢ МЕТАБОЛИЗММЕН БАЙЛАНЫСТЫ МАЙ АУРУЫ

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Түйін:
Кіріспе. Халықтың қартаюына байланысты бүкіл әлемде егде жастағы адамдарда метаболикалық бұзылыстардың таралуы, бауырдың майлану ауруының даму қаупі едәуір артуда. Қазіргі уақытта метаболикалық себепті туындаған бауырдың майлану ауруы - бауыр ауруларының кең таралған себебі, бұл ауру бұрын бауырдың алкогольді емес майлану ауруы аталған. Бұл ауру семіздік, 2-типті қант диабеті және дислипидемия секілді метаболикалық бұзылыстармен тығыз байланысты. Ағымдағы бағалау бойынша, аталған аурудан ересек жастағы халықтың 24% зардап шегеді, бұл бүкіл әлемдегі адамдардың бір миллиардын құрайды.
Мақсаты. Егде жастағы популяциядағы бауырдың метаболизммен байланысты май ауруының аурушаңдық құрылымын талдау және егде жастағы адамдар тобында осы аурудың таралуы мен өліміне әсер ететін бауырдың қартаю механизмдерін анықтау.
Материал және әдістер. Осы әдеби шолуда біз 32 ғылыми жарияланымдарға талдау жасадық, оларға 2012 жылдан 2024 жылға дейінгі 13 жылдағы соңғы шолулар, түпнұсқалы мақалалар мен мета-талдаулар кіреді. Әдеби тұрғыдағы ізденіс Google Scholar, Web of Science, PubMed, Scopus және Abridged Index Medicus секілді деректер қорларын пайдаланумен іске асырылды.
Нәтижелер. Бізге қол жетімді әдебиеттерді зерттеу барысында бауырдың май ауруының таралуы ерлерде 40-50 жаста және әйелдерде 60-69 жаста шыңына жететіні анықталды, көбінесе егде жастағы (>75 жаста) когорттарда төмендейді, дегенмен бауырдың май ауруының таралуына және егде жастағы популяциядағы фиброзбен байланысына тікелей әсер ететін деректер жоқ.

Қорытынды. Егде жастағы адамдар арасында метаболизммен байланысты бауыр ауруының таралуы туралы қарама-қайшы дәлелдер бауырдағы жасқа байланысты өзгерістердің механизмдерін түсіну үшін қосымша зерттеулер жүргізу қажеттілігін көрсетеді. Егде жастағы адамдарда бұл ауруды зерттеу өмір сүру сапасын жақсартуға, медициналық көмекті оңтайландыруға және алдын алу мен емдеу Стратегияларын жасауға үлкен мән береді.
Түйінді сөздер: бауырдың алкогольсіз май ауруы, бауырдың метаболизммен байланысты май ауруы, бауырдың майлы дистрофиясы, егде жас, қартаю, таралуы

МЕТАБОЛИЧЕСКИ-АССОЦИИРОВАННАЯ ЖИРОВАЯ БОЛЕЗНЬ ПЕЧЕНИ У ЛИЦ ПОЖИЛОГО ВОЗРАСТА

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Резюме
Введение. В связи со старением населения во всем мире распространение метаболических нарушений, риск развития жировой болезни печени у лиц пожилого возраста значительно возрастает. В настоящее время метаболически-ассоциированная жировая болезнь печени является наиболее распространённой причиной заболеваний печени, которая ранее имело название неалкогольная жировая болезнь печени. Данное заболевание тесно связано с метаболическими нарушениями такими как ожирение, сахарный диабет 2 типа и дислипидемия. По текущим оценкам, ею страдают 24% взрослого населения, что составляет один миллиард человек во всем мире.
Цель исследования. Проанализировать структуру заболеваемости метаболически-ассоциированной жировой болезни печени в пожилой популяции и определить механизмы старения печени, влияющие на распространённость и смертность от данного заболевания в пожилой когорте.
Материалы и методы исследования. В данном литературном обзоре мы провели анализ 32 научных публикаций, которые включали обзоры, оригинальные статьи и метаанализы, опубликованные за последние 13 лет с 2012 по 2024 годы. Литературный поиск осуществлялся с использованием баз данных, таких как Google Scholar, Web of Science, PubMed, Scopus и Abridged Index Medicus.
Результаты. В ходе исследования доступной нам литературы было обнаружено, что распространённость жировой болезни печени достигает пика в возрасте 40–50 лет у мужчин и 60–69 лет у женщин, часто снижаясь в более старших (>75 лет) когортах. Выявлены механизмы старения клеток печени, оказывающих влияние на течение данного заболевания в пожилом возрасте, однако отсутствуют данные о прямом влиянии на распространённость и связь с фиброзом в пожилой популяции.
Выводы. Противоречивые данные о распространённости метаболически-ассоциированной жировой болезни печени среди лиц пожилого возраста подчеркивают необходимость дальнейших исследований для понимания механизмов, лежащих в основе возрастных изменений в печени. Изучение данного заболевания у пожилых людей имеет большое значение для улучшения качества жизни, оптимизации медицинской помощи и разработки стратегий профилактики и лечения.
Ключевые слова: неалкогольная жировая болезнь печени, метаболически-ассоциированная жировая болезнь печени, жировая дистрофия печени, пожилой возраст, старение, распространённость

Background. According to the World Health Organization (WHO), in 2022, every eighth person in the world suffered from obesity, while overweight was observed in 2.5 billion adults (aged 18 years and older), of which 890 million people were obese. WHO also notes that most of the world's population lives in countries where more people die from overweight and obesity than from underweight [1]. According to Jeeyavudeen M. et al. (2023), obesity is directly associated with various metabolic disorders, in particular, metabolic-associated fatty liver disease (MAFLD) and type 2 diabetes mellitus (T2DM) [2].
The global prevalence of fatty liver disease has recently increased, along with metabolic syndrome, which are independent important factors of mortality and morbidity worldwide [3]. Since 2020, experts from 22 countries led by Yeslam M. have proposed to change the terminology from non-alcoholic fatty liver disease (NAFLD) to metabolic-associated fatty liver disease (MAFLD) [4], which is comprehensive and simple, as well as independent of other liver diseases, and more effectively emphasizes the pathogenic role of metabolic dysregulation in the onset and progression of this debilitating liver disease [5]. Since the introduction of “MAFLD” as an alternative term with its own set of diagnostic criteria, there have been more than 800 unique articles citing the new diagnosis [6].
Currently, MAFLD is the most common cause of liver disease. According to current estimates, it affects 24% of the adult population, which is one billion people worldwide [7,8].
Metabolic-associated fatty liver disease is a multisystem disease closely associated with metabolic risk factors such as diabetes mellitus, dyslipidemia, hypertension, and obesity. These risk factors are known to be higher in the elderly [8]. Diagnosis, treatment, and prevention of socially significant diseases in the elderly are sometimes complex, and healthcare professionals should take into account certain age-related factors. In this review, we aimed to evaluate the impact of age-related liver changes on the prevalence of MAFLD in the elderly and age-related mortality risks (age >65 years). Most of the studies mentioned in this review were conducted before the terminology change, and the diagnostic criteria were largely based on the definition of NAFLD. In 2021, *Wong V. et al.* (2021) conducted a study in Hong Kong that showed that the new definition of MAFLD did not significantly change the prevalence compared with NAFLD, and therefore we used the new terminology in our review. According to the above-mentioned study, 89.2% of the diagnoses met both NAFLD and MAFLD criteria, and 5.8% and 5.1% met only MAFLD and NAFLD criteria, respectively [9]. However, studies on the prevalence of MAFLD in the elderly are scarce in the available literature, and the results of the studies are inconsistent, indicating the need for further study on this topic.

Purpose of the study. To study the prevalence of metabolic-associated fatty liver disease in elderly individuals and the mechanisms of liver aging that affect the course of this disease.

Materials and research methods. The analysis was performed using 32 full-text reviews, original articles and meta-analyses published over the past 13 years from 2012 to 2024. The literature search was performed using databases such as Google Scholar, Web of Science, PubMed, Scopus and Abridged Index Medicus. The search used keywords from Medical Subject Headings (MeSH), such as: "non-alcoholic fatty liver disease", "metabolic-associated fatty liver disease", "fatty liver degeneration", "old age", "aging", "prevalence".

Historical overview of fatty liver nomenclature

The term "fatty liver" was first described by Thomas Addison (England) in 1836 [10]. Subsequently, Karl Rokitansky, a pathologist from Vienna (Austria), noted in autopsy specimens that fat accumulation in the liver could be a cause of cirrhosis [11]. In 1884, Pepper first reported fatty infiltration of the liver in a patient with diabetes, and already in 1885, Bartholow made one of the earliest observations of a potential association between obesity and fatty liver [12]. Further, in 1938, Charles Connor described an association between fatty liver and the progression of cirrhosis in patients with diabetes [13]. In 1958, Westwater and Feiner reported histological findings of fatty infiltration of the liver in obese patients [14]. In 1962, Thaler added an additional clinical and pathological description of the disease [14]. Since then, several reports in the 1950s–1970s pathologically documented similarities between alcoholic liver disease and the histopathological liver changes seen in obese, diabetic patients [14]. In 1980, Jurgen Ludwig described a series of 20 patients who denied alcohol abuse but had chronic liver disease with histological features of alcoholic fatty liver disease. At the time, the disease had no name and Ludwig coined the terms "NAFLD" and "non-alcoholic steatohepatitis" (NASH) to describe the liver pathology [15]. In 1983, Moran et al. described a series of 3 children with obesity and steatohepatitis [16]. Since then, for 40 years, the disease has remained with the prefix "non", implying that it is simply an exception to the underlying condition. At the same time, in clinical practice, this condition has become a leading cause of liver disease and liver transplantation. Since its initial description, clinical and research interest in MAFLD has increased with numerous studies documenting its heredity, natural history, and highlighting the pathophysiological relationship with features of the metabolic syndrome, hepatic and extrahepatic complications [17-19]. This research has led to advances in our understanding of the causes and pathogenesis of MAFLD, has led to a flurry of clinical trials of drug treatments, and has simultaneously highlighted that NAFLD is an incorrect term to describe a liver disease associated with metabolic dysfunction.

Aging as a risk factor for the development of MAFLD

Population ageing is a worldwide problem with significant implications for public health, social welfare and economic development. Ageing is a complex biological process that involves a gradual deterioration of various physiological functions and the accumulation of molecular and cellular damage over time [20]. Aging of the body, including the liver, is accompanied by progressive physiological changes in which the efficiency and regulation of cellular processes decreases [21]. Such hallmarks of ageing include genomic instability, epigenetic changes, telomere attrition, impaired proteostasis, impaired nutrient uptake, mitochondrial dysfunction, stem cell depletion and altered intercellular communication (Figure 1).

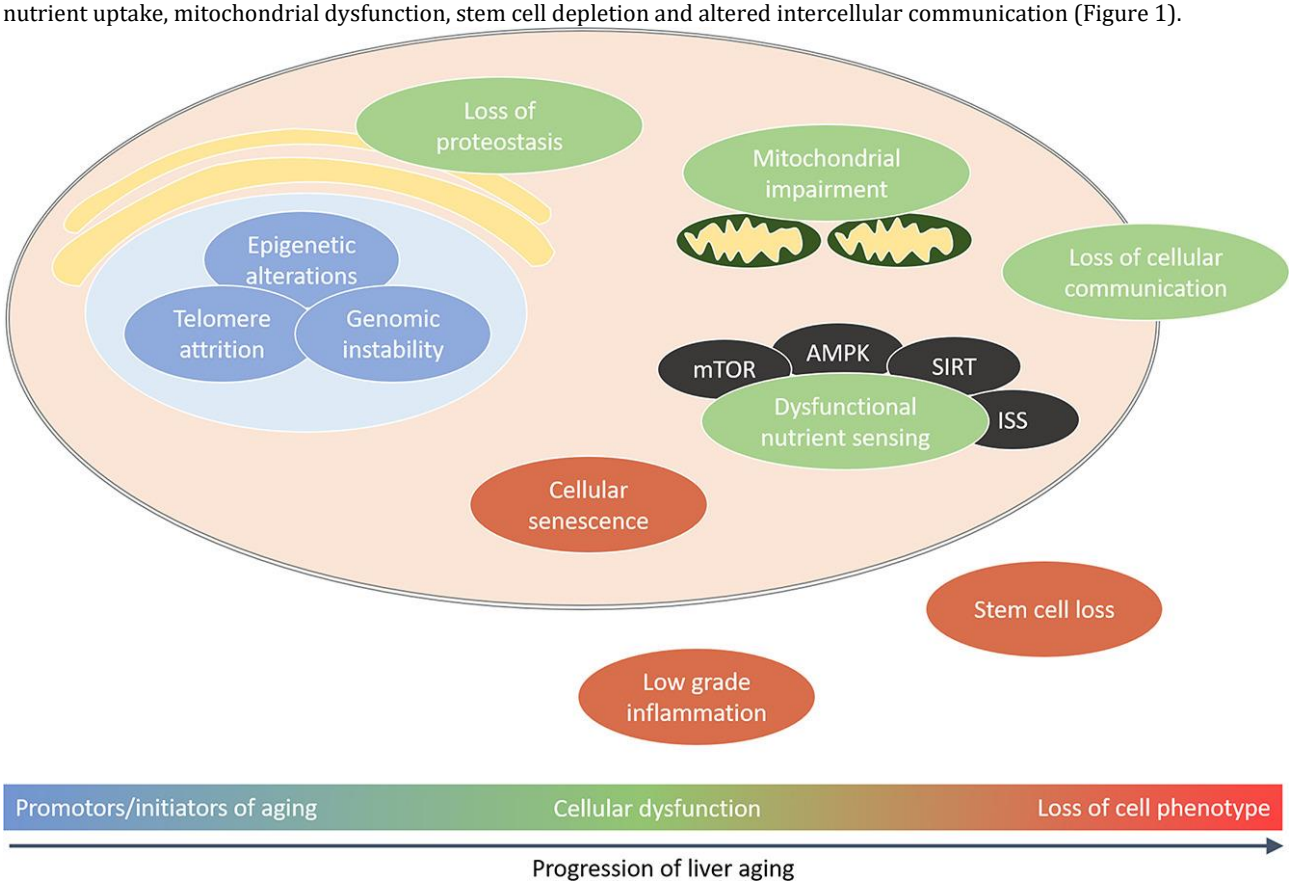

Figure 1 – Progression of liver aging

Abbreviations: AMPK: 5'-adenosine monophosphate-activated protein kinase; ISS: insulin/insulin-like growth factor 1 signaling system; mTOR: mammalian target of rapamycin; SIRT: sirtuin.

The liver's ability to regenerate also declines with age. As cells age, they become insensitive to mitogenic stimuli and less prone to apoptosis, which is associated with multiple cellular and molecular changes and various phenotypic alterations, including stable proliferation arrest [22]. Cellular senescence can impair tissue repair and regeneration, thereby contributing to aging. Aging-associated changes in liver cells include volume changes, polyploidy, accumulation of dense bodies (lipofuscin) inside liver cells, decreased smooth endoplasmic reticulum area, and decreased mitochondrial number and dysfunction [23]. Some studies also suggest that telomere attrition and shortening, oxidative stress, and DNA damage occur in older individuals as a result of accumulated cycles of various cellular injuries and repairs throughout life. This leads to irreversible cessation of cell growth and disruption of proliferation, which can ultimately lead to liver cirrhosis [24]. However, the natural aging process does not directly affect hepatocytes and cholangiocytes, and telomere shortening is characteristic exclusively of Kupffer cells and stellate cells, so this phenomenon requires further study [25].
According to *Yalei Zhao et al*. (2022), liver aging is the result of the accumulation of senescent hepatocytes, in which the number of hepatocytes decreases, the regenerative capacity of the liver deteriorates, and polyploid hepatocytes accumulate [26]. Aging leads to increased triglyceride levels and a decreased ability to utilize and break down triglycerides (Figure 2) [27], which are important causes of MAFLD.

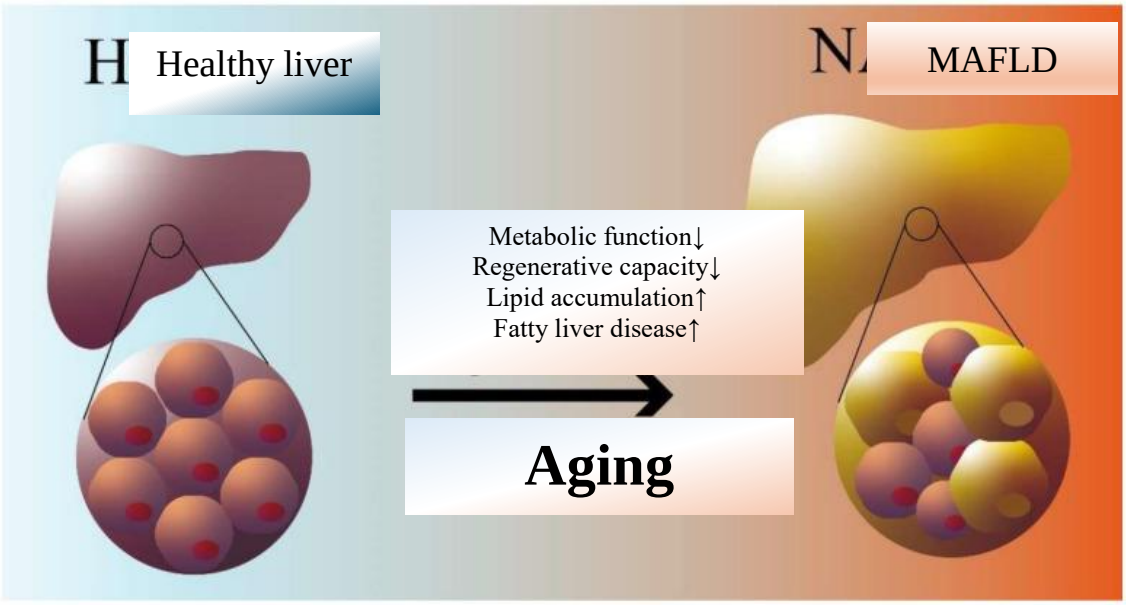

Figure 2 **- Aging and MAFLD. Impaired lipid metabolism and liver regeneration leads to accumulation of lipids in the liver and steatosis (→ related to the aging process).**

Ghavimi S. et al. (2019) believe that with aging of the hepatobiliary system, the risks of developing various liver diseases may increase, which subsequently may serve as an unfavorable prognostic factor causing an increase in mortality [23].

Comparative assessment of the prevalence of MAFLD in middle (45–60 years) and elderly (60–75 years) age
According to the definition of WHO and the United Nations (UN), middle age is the period from 45 to 60 years, followed by old age, which is divided into 3 periods: elderly (60-75 years), advanced (75-90 years) and longevity (over 90 years) [28]. Although risk factors for the development of MAFLD, such as hypertension, diabetes, dyslipidemia and obesity, are higher in older people, according to the study by Alqahtani SA et al. (2021) in a cohort of patients aged 40 to 70 years, the prevalence of MAFLD is slightly higher than in the cohort over 70 years, which corresponds to an "inverted U-shaped curve". Thus, the prevalence of MAFLD peaks in middle age and declines from that point on, resulting in a lower prevalence of MAFLD in older patient cohorts compared to younger cohorts [8].
In their study, *Lin S et al*. (2020) compared patients with NAFLD and MAFLD, where the authors showed that patients with MAFLD were older than those with NAFLD (48.39 ± 15.20 vs. 46.81 ± 15.77 years, $p < 0.001$) [29].
At the same time, the authors *Wong V et al*. (2021) also noted in their study that the prevalence of MAFLD increased with increasing age and ranged from 11.7% among patients under 30 years of age to 40.9% among patients over 60 years of age. The prevalence of NAFLD had a similar trend: from 13% to 39.1%, respectively [9].
A study by *Koehler E.M. et al*. (2012) in Rotterdam among 2811 elderly people reported a prevalence of MAFLD of 39.6%, 32.1% and 21.1% at the age of 75–79, 80–84 and >85 years, respectively [30].
Also, a cross-sectional study by *Noureddin M et al*. (2013) in the USA, which included 61 patients ≥65 years old and 735 young and middle-aged people (18-64 years), revealed a higher prevalence of advanced fibrosis in elderly patients with MAFLD than in young patients (44% versus 25%) [31]. A study by *Hartleb M et al* (2017) in Poland showed a decrease in the prevalence of MAFLD in people ≥80 years old to 37.2%, compared to 68.7% in those <80 years old [32].
A study by *Tsung-Po Chen et al*. (2020) conducted among the elderly population of Taiwan, China aged ≥65 years found a prevalence of 41.9%, a decrease in the prevalence of MAFLD with age, from 45% in those aged 65–70 years to 31.8% in those

aged >80 years, diagnosed by ultrasound, was found. A logistic regression analysis was also conducted in the elderly, where age was found to be negatively associated with fatty liver [33].

Also, *Yu-ling Chen et al*. (2021) reported in their study that the overall prevalence of MAFLD was 23.8% and a significant difference was found between men and women in the prevalence of MAFLD (men: 32.3%, women: 13.4%). For the entire population, the prevalence tended to increase with increasing age and then decreased, with a peak prevalence of 34.5% in the age range of 55–59 years [34]. A similar study was conducted by *Yuan Q et al*. (2022), where they described that the overall prevalence of MAFLD was 32.4% (23,832/73,566). They also noted that there was a prevalence difference between men and women (36.80% vs. 28.65%, p < 0.001). The prevalence of MAFLD in men and women increased with age (p < 0.001). The prevalence of MAFLD in men peaked at 40–49 years of age and then began to decline. MAFLD was more common in women than in men after 50 years of age [35].

A study conducted in Japan by *Marenao Tanaka et al*. (2022) showed that the prevalence of MAFLD was 42.7% among 627 study participants with a mean age of 65 years (range 19–98 years, median 68 years). The incidence of MAFLD was higher in women (45.4%) than in men (39.7%) [36]. *ZHUANG Yingjie et al*. (2023) in their recent study in Beijing, China, conducted a detailed analysis of the prevalence of MAFLD, where 2,825 middle-aged and elderly patients with a mean age of (71.62 ± 11.29) years were examined, where men accounted for 95.8% (2,705 cases). The prevalence of MAFLD was 55.5%, with a higher incidence in men than in women (56.0% vs. 45.5%, P=0.031). The prevalence rates in patients aged 45-59, 60-69, 70-79, and ≥80 years were 45.1%, 58.9%, 59.9%, and 53.0% (P<0.05), respectively. Moreover, multivariate logistic regression analysis showed that the risk of developing MAFLD in patients aged 60-69, 70-79 and ≥80 years was 1.953 (95% CI: 1.490-2.559), 2.029 (95% CI: 1.522-2.707) and 1.722 (95% CI: 1.279-2.317) times higher than in 45-59 years, respectively. Also, the risk in patients with obesity and overweight was 23.131 (95% CI: 14.451–37.025), which is 6.232 (95% CI: 5.170–7.512) times higher than in patients with normal weight [37].

Qingdan Liu et al. (2023) compared the prevalence of NAFLD and MAFLD in a general population from Southeast China, involving 6,718 participants. The mean age of the participants was 57 years (range, 50–65 years), of whom 2,330 were diagnosed with MAFLD, yielding a prevalence rate of 34.7% [38].

Also, *Grace En Hui Lim et al*. (2023) conducted a meta-analysis of observational data on the differences in prevalence and risk factors between MAFLD and NAFLD, involving 379,801 patients. The mean age of patients with MAFLD was 54.49 years (95% CI, 51.73–57.40 years). The overall prevalence of MAFLD was 39.22% (95% CI, 30.96%–48.15%) with the highest prevalence in Europe (54.53%; 95% CI, 34.76%–72.98%, n=12,070) and Asia (39.89%; 95% CI, 30.26%–50.37%; n=330,378), followed by North America (29.08%; 95% CI, 22.17%–37.12%; n=36,120). The current definition of MAFLD accounts for only 81.59% (95% CI, 66.51%–90.82%) of NAFLD diagnoses. Patients had increased odds of being diagnosed with MAFLD compared with NAFLD (odds ratio, 1.37; 95% CI, 1.16–1.63; P < .001). MAFLD was significantly associated with males, higher body mass index, hypertension, diabetes, lipids, transaminitis, and higher fibrosis scores compared with NAFLD [39].

In 2024, a cross-sectional study was published by *Yajun He et al*. in China, which aimed to investigate the prevalence of MAFLD, its various metabolic comorbidities, and their potential risk factors. The study included 9171 people, among whom 2081 had MAFLD, accounting for 22.69% (95% CI: 21.84–23.56). Among the MAFLD population, 621 (29.84%), 663 (31.86%), 471 (22.63%), 111 (5.33%) cases had one or two or three or four comorbidities respectively, while only 215 (10.33%) had no comorbidities. Moreover, those aged 60 years and above showed a significantly lower proportion compared to other age groups among those with MAFLD without comorbidities (5.87% vs 10.77%, 11.78%, P < 0.05). Most of the individuals with MAFLD in all age groups had comorbidities, accounting for more than 80% of the total [40].

Conclusions. Aging is a natural process that requires adaptation of medical care and consideration of treatment. Since the prevalence of MAFLD increases with age and complications associated with MAFLD may represent an important source of morbidity and health care utilization, this disease should be considered in the elderly.

Summarizing all the above data of the cited literature, it is obvious that the prevalence of MAFLD in the elderly is high, which undoubtedly requires the adoption of comprehensive strategies to raise awareness and address all aspects of MAFLD at the local, regional and global levels.

Despite the fact that the impact of such diseases as hypertension, diabetes, dyslipidemia and obesity on the course of MAFLD increases with age, studies show a decrease in the prevalence of this disease in the cohort of elderly patients.

The mechanisms of age-related liver changes that affect the course of MAFLD in old age have been identified, such as: decreased liver regeneration capacity, shortening of telomeres, damage to genomic and mitochondrial DNA. At the same time, it is currently impossible to reliably state whether this is due to the fact that patients with MAFLD die earlier than patients without MAFLD, the so-called “survivorship bias,” or whether this is a consequence of lifestyle and nutritional changes at an older age.

Multiple metabolic disorders, especially obesity, should be given more attention for the prevention and better management of MAFLD. More research is needed to determine the potential mechanisms underlying the occurrence of MAFLD and to better understand the relationship and causality between MAFLD and multiple metabolic disorders, which will provide important insights for the prevention and treatment of MAFLD. Because we understand the global burden of MAFLD and cannot definitively say how mechanisms of liver aging influence the course, prevalence, and mortality of MAFLD in the elderly population, further epidemiological and mechanistic studies, as well as efforts to not exclude older people from clinical trials, will be needed to understand the best approach to diagnosing and treating MAFLD in the elderly.

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