Morphological and Functional Changes in Hepatic System Precipitate Liver Disease in Elderly: Addressing Knowledge Gaps and Treatment Challenges

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ABSTRACT

Globally, the elderly population are more increasing each year. The enhancement of life expectancy is also followed by the enhancement of chronic illness, which one of them is liver disease. In elderly, there are also several physiological and biochemical changes in liver. Several studies show that the reduction of liver function will affect the severity of liver clinical manifestation in older people. This review article aims to discuss more about liver disease in older population. Hepatitis A in elderly has higher mortality and morbidity rates compared to young people. More over, the progressivity of acute hepatitis B to chronic hepatitis B is also greater in older people than young people. The treatments of hepatitis B and hepatitis C are safe and effective to be applied in elderly. Polypharmacy and frailty affects the elderly to be more susceptible to drug induced liver injury (DILI). This review aims to address knowledge gaps in understanding the morphological and functional changes in the aging hepatic system, their implications for disease progression, and the effectiveness of current therapeutic strategies. By critically analyzing recent evidence, we identify challenges in treating liver diseases in the elderly and highlight areas requiring further research.

Keywords: *Elderly, hepatocellular call carcinoma, liver disease*

ABSTRAK

Setiap tahun, jumlah populasi lanjut usia terus meningkat. Peningkatan usia harapan hidup ini juga diikuti oleh peningkatan angka kejadian penyakit kronis. Salah satunya adalah penyakit hati kronis. Pada lanjut usia, angka kematian akibat penyakit hati kronis lebih tinggi dibandingkan usia muda. Fungsi fisiologis dan biokimia organ hati akan menurun pada usia lanjut. Beberapa penelitian menyimpulkan penurunan fungsi organ hati ini akan memperberat menifestasi klinis penyakit hati pada orang lanjut usia. Pada review artikel ini akan membahas secara mendalam mengenai penyakit hati pada pupulasi lanjut usia. Pada orang lanjut usia yang mengalami hepatitis A memiliki morbiditas dan mortalitas lebih tinggi. Terapi hepatitis B kronis dan hepatitis C efektif untuk digunakan pada lanjut usia. Polifarmasi dan frailty menyebabkan populasi lanjut usia lebih rentan mengalami DILI. Artikel ini bertujuan untuk memahami perubahan morfologis dan fungsional pada sistem hati yang terjadi pada usia lanjut, dampak terhadap perkembangan penyakit, serta efektivitas terapi.

Kata Kunci: *Usia lanjut, karsinoma hepatoseluler, penyakit hati*

INTRODUCTION

People who are aged 65 years and over achieved 703 million persons. The population will be estimated double to be 1,5 billion persons in 2050. Globally, the number of older people increased from 6% in 1990 to 9% in 2019. More over, it will be estimated to be 16% in 2050.[1] According to Badan Pusat Statistik (BPS), the population of older people attained 16,07 million persons or 5,95% of total population in Indonesia.[2]

As the number of older people increased, the incidence of chronic illness also increased such as cardiovascular disease, cerebrovascular disease, cancer, and liver disease.[3] According to Su et al, the mortalilty rates of older people are 12 higher than younger persons.[4] These are due to anatomical structure alterations in older people. Aging is connected to structural and functional changes included blood volume, blood supply, and liver endothelial function. Therefore, there must be particular clinical approach in older people.[5]

Despite the growing body of literature, key knowledge gaps persist. This review highlights recent evidence on how morphological and functional changes in the liver influence disease progression, emphasizing the importance of tailoring treatments to ensure effectiveness and safety in elderly patients. It aims to address existing knowledge gaps and offers recommendations to advance research and improve clinical practices.

CELLULAR AND BIOCHEMICAL CHANGES IN GERIATRIC POPULATION

The Reduction of Liver Volume and Blood Flow in Hepatocyte

As the people are getting older, there would be changes in liver volume and liver blood flow. Based on ultrasound examination, there is a degradation in liver volume for about 20-40% in geriatric population.[5] Not only does a reduction in liver volume, but also the blood flow reduces about 35% in older people compared to young people who aged 40 years.[5] The hepatocytes in older people show a degression in mitochondria cells, but an enhancement of mitochondria volume.[6] Due to mitochondria cell reduction, the hepatocytes are susceptible to damage and decreased regeneration functions.[6]

The Accumulation of Lipofuscin

Lipofuscin, wear and tear pigment, is one of the most often pigment found in liver biopsy in geriatric population. Hepatocytes in older people have more solid compartment like secondary lysosome and lipofuscin than hepatocytes in younger persons. The accumulation of lipofuscin is asscociated with oxidative stress which occurs chronically and cell failure to degrade denaturated protein.[6] This process will also interfere cellular mechanism because lipofuscin apprehend cation which provide the free radicals. Lipofuscin presents non-enzymatic activity such as glycosylation and cross-linked of heterogeneous cellular components, included nucleic acid, protein, and fat. The accumulation of lipofuscin will interfere the transcription process of hepatocyte genes and reduce cell survival.[8]

The Morphological Changes in Liver Sinusoid

Several studies are showing that aging will affect the hepatocyte function through several morphological changes in sinusoidal vascular system. In geriatric population, the Liver Sinusoidal Endothelial Cells (LSECs) become thicker 50% whereas the fenestrated diameter of sinusoidal endothelial vascular will decrease.[9] The reduction of fenestrated endothelium induces the deposit of lipoprotein-like chylomicroin in hepatocyte. This accumulation process leads to decrease the effectivity of waste disposal and induces the autoimmune disease which affect the interaction of T-lymphocytes and hepatocytes.[5] The degradation of LSECs waste disposal induces to dysregulation of LSECs to acute and chronic illness which enhance the risk of illness related to age, like diabetes mellitus, arteriosclerosis, arthritis, and neurodegenerative disease.[9,10]

The Transformation of Stellata Hepatic and Kupffer Cell

Stellata hepatic is a perisit cell in hepatocytes which functionate as the storage of vitamin A and lipid and also as the regulation of matrix extracellular metabolism. This perisit cell will induce the sinusoidal blood flow through contractile mechanism in stelata hepatic. In the animal study of primates and rats showed that there was an enhancement of lipid in stellata hepatic using the electonical microscope. [9,10]

Kupffer cells are liver macrophage in sinusoidal lumen. Kupffer cells produce the inflammatory mediators like TNF-α and IL-6 as the innate immune

response. Not only does produce the inflammatory mediators, Kupffer cells also do a phagocytosis of macromolecules which are massive to be put in liver sinusoidal endothelial cells. These had been proven in rats study that Kupffer cells in older rats showed the reduction of phagocytosis and autophagy and the enhancement of cytokine production which contributed to the inflammatory process in hepatocyte (inflammaging).[7,9]

DRUG METABOLISM CHANGING IN GERIATRIC POPULATION

In geriatric population, the first metabolism in liver (first-hepatic uptake) degrade because of the reduction of liver volume and blood flow.[8] Drug metabolism in people aged over 70 years old will decrease about 30%. The reduction of P-450 cytochrome has a contribution to the downgrade of drug metabolism. As a result, drugs (midazolam, phenytoin, propranolol, and acetaminophen), which are excretion and metabolism by P-450 cytochrome (CYP) will decrease. Therefore, geriatric population have higher risk in Drug Induce Liver Injury (DILI) than younger population.[11]

According to Rana et al, the second drug metabolism are not affected to the age. A study showed that there was no correlation between older people and glucuronidation and sulfation process in human.[12] Another study showed that there was no correlation between hippuric acid formation and glutathione concentration with older people.[13] More over, the distribution volume of drug water soluble reduce in geriatric population because of the escalation of lipid-water ratio so that there will be drug accumulation in geriatric population.[11,14]

LIVER DISEASES IN GERIATRIC POPULATION

HEPATITIS A

Globally, hepatitis A incidence increased 13,9% from 139,54 million cases in 1990 to 158,94 million cases in 2019.[15] A study showed that Indonesia had very high hepatitis A seroprevalence, 90%, which mostly occurred in young child 10 years old. The incidence of hepatitis A in older people is fewer rather than young patients because they have already been immuned to hepatitis A.[16] Nevertheless, the hospitalization rate, hepatitis A complication, and mortality rate are 10 times greater in older people than in young people.[8] According to National Health and Nutrition Examination Survey (NHANES) found that there was a degradation of HAV immunity rates in people aged 50-59 years.[17] Therefore, Advisory Committee on Immunization Practices United States recommends to give hepatitis A vaccine as soon as possible to people aging 40 years and over who travel to endemic region. If older people travel to endemic area in less than 2 weeks, they should have double shot protections which are hepatitis A vaccine and immunoglobulin in different injection site.[18]

HEPATITIS B

According to WHO, there were 296 million persons who lived with chronic hepatitis B in 2019. There are also 1,5 million persons infected to hepatitis B annually. The mortality rates of hepatitis B estimate 820 million cases because of deadly complications which are liver cirrhosis and hepatoma.[2] In Indonesia, each prevalence of HbsAg, anti-HBc, and anti-HBs reached 7,1%, 31,9%, and 35,6% in 2013. HBsAg prevalence declined from 9,4% in 2007 to 7,1% in 2013. Therefore, the endemic status of HBsAg in Indonesia transformed from severe to moderate.[19] Older people are one of the mortality predictor factors of hepatitis B infection.[20]

Clinical Manifestations

During acute hepatitis B epidemic in Japan, there were no significant symptoms unless some of older people had mild symptoms such as jaundice, nausea, and vomiting.[21] Hepatitis B progression was inversely propotional to the age of first infection. The highest progression occurred in infants reaching 90% and over. Half of hepatitis B progression occurred in child 1-5 years estimating 25-50%. Ultimately, older children had few progression reaching 5% of total cases.[22] Unfortunately, the chronic hepatitis B progression mostly occurred in older people. According to Kondo et al, more than half total patients of chronic hepatitis B progression were older people.[21] There were differences of HBsAg seroclearance between older patients and young adult patients. Older people had HBsAg seroclearance twice higher than young adult people which were appropriated with several variables such as, gender, HBV-DNA baseline, Alanin Aminotransferase (ALT), ethnicity, and Body Mass Index (BMI).[23] Positive HBeAg in people aging 60 years were four times lower than in young adult people with age range 30 -39 years old.[24]

Older people infected to hepatitis B had the same HBeAg level with young people which were 77 percent. However, there were significantly anti-HBe between older people and young adult, 5,5% vs 18,6%.[25] A multicenter study in United States showed that untreated hepatitis B patients aging 40 years old had HBV-DNA serum 2,5 times higher rather than younger people (HBV genotype A,B,C,D,E,F, and G).[26] A cohort study in Asia described that HBV-DNA genotype B and C in older people had lower rates than young adult people aging 30 -59 years.[27] Cirrhocis progression has a correlation factor with HBV-DNA level, but the most important risk factors are age and men gender.[28]

Treatments

The standard regimens of hepatitis B have the same efficacy with the pegylated interferons both in older people and young adult people.[22] Lamivudine has similar efficacy to geriatric patients and young patients based on HBV percentage reduction. However, both group of people are susceptible to viral resistance thus lamivudine is restricted to use because of the secondary high resistance.[29] Nucleotide Analogs such as tenofovir, entecavir, and adefovir, have been lower resistance but higher reccurence in older people than in young adult people. Therefore, geriatric patients infected hepatitis B need to have a long term therapy.[22] Interferon has better clinical outcomes in people aging 37 years old than young adult people.[30]

Vaccination

Aging is asscociated with the derivation of immunity response to vaccination. The immune response in people aging 70 years old and over of hepatitis B vaccine are lower than population aging less than 60 years old (70% vs 98%).[31,32] T-cell dysfunction is one of the main factors affecting immune response declined in older people.[33] Growth factors (granulocyte-monocyte colony stimulating factor) intend to resolve T-cell dysfunction problem in declining immune response of hepatitis B vaccine. This treatment plays a role as adjuvant therapy to increase seroprotection.[34] In pilot research, there was no difference clinical effect between adjuvant therapy (granulocyte-monocyte colony stimulating factor) and immune response of hepatitis B vaccine in older people.[33]

HEPATITIS C

The Prevalence and Clinical Manifestation

In 2020, the prevalence of hepatitis C achieved 56,8 million persons all over the world. During 2013-2016 in the United States, almost 2 million persons infected by chronic hepatitis C.[35] According to Riskesdas in Indonesia, the prevalence of anti-HCV achieved 0,82% whom the highest population were the older people range aging 50-59 years old and 60 years old.[19] There are several risk factors of hepatitis C infection such as blood transfusion, injection use, tattoo, hemodialysis, and health workers.[8] In older people who are infected by hepatitis C, the incidence of liver fibrosis is higher rather than young people although older people have normal baseline of ALT. This process allows that the liver fibrosis is earlier occurred in the first hepatitis C infection of older people.[36] The median time of cirrhosis is 33 years after the first infection of hepatitis C.

The median time of cirrhosis after the first infection of hepatits C is 33 years with age range 21-30 years old while the median time of people aging 40 years is 16 years. This shows that the median time of cirrhosis occurred in older people are earlier than in younger people.[37] There is no evidence about the serologi marker to prove hepatitis C in people 80 years old, but a study shows that the serology marker does not relate to the age. Therefore, the non-invasive serological test in older people can be used as an instrument to diagnose hepatitis C although they have normal ALT.[36]

Treatments

The treatments of hepatitis C have good outcomes in older people. In a cohort study, the successful rates of Sustained Virologic Response (SVR) attain 96,7%. Even though the incidence of cirrhosis is higher in older people than younger people, The SVR in older people is the same as the younger people.[38] Cirrhosis, low albumin, high creatinine value are prognosis indicators of hepatitis C which are worse in older people.[38] The successful rates of Direct Acting Antiviral (DAA) in people aging between less than 65 years and 65 years are 98% and 91%.[39] Sofosbuvir is effective to treat hepatitis C in older people. Older people in sofosbuvir tretatment have the same sustained virologic response as younger people. Other than that, this treatment is safe to use in older people.[40] The medical reconciliation is necessary to reduce drug interactions in older people infected HCV.[39] According to Kamel et al, there is no

correlation between age and the successful treatment of DAA in older people. DAA is secure enough to use in older people.[41] The first year and the third year incidences of hepatocellular carcinoma (HCC) are no significant different between older people and younger people.[42] The first and third year survival rates of hepatitis C infection in older people which is treated by DAA is 100% and 95,6%. It's not significantly different compared to patient ages<75 years.[42]

DRUG INDUCED LIVER INJURY (DILI)

Definition

Drug Induced Liver injury (DILI) is an acute or a chronic liver defect after using medicines, herbs, and dietary supplements.[43,44] DILI consists of 2 types, instrinsic and idiosyncratic. Instrinsic DILI is a liver defect after using high dose of medicines or herbs, such as acetaminophen while Idiosyncratic DILI is a rare disease that develops independently of drug dose and dietary supplements in human.[44]

Epidemiology

The incidence of DILI in older people is higher compared to younger people. DILI incidence achieves 76,33 of 10.000 persons who are aged 65 years or over. 86,84% of total cases are older people consumed more than four drugs.[45] A study shows that the incidence of DILI overall achieves 9 per 100.000 persons in people aging 15-29 years old. The incidence of DILI increases 41 out of 100.000 persons in older people.[46]

The Modification Of Pharmacokinetics and Pharmacodynamics

There are several physiologic changes in older people, such as water derivation, lean body composition reduction, and lipid enhancement. These changes affect to enhancement in distribution volume of lipophilic drugs and prolong half-life. If the lipophilic drugs are given to older people, they probably have more side effects in liver rather than young people.[14] Drug biotransformation mostly occurred in liver, although the other organs also involved to drug metabolism, such as kidney, gastrointestinal tract, lung, and skin. Aging reduces liver volume and blood flow so that drug elimination process could reduce in liver. The reduction of bile flow and secretion is also asscociated to aging.[44] Furthermore, frailty and polypharmacy affect to DILI in older people.[14,47]

Screenings and treatments

The enhancement of ALT and total bilirubin is the main biomarker to detect liver defect. ALT serum is more specific than AST. Moreover, ALT is very sensitive to detect liver failure. However, biomarker enhancement is very difficult to distinguish from other liver diseases.[44] DILI can be diagnosed by excluding any other reasons of ALT enhancement. The diagnosis of DILI should be any 1 of the following, >5 fold increase over the upper limit of normal for ALT, or >2 fold increase over the upper limit of normal for ALP, or >3 fold increase of ALT and >2x fold increase of bilirubin.[12,48,49]

The first thing to do after suspecting patients with DILI is to stop using current medicines. Most of DILI cases will resolve completely, but some of them will progress into acute liver failure and fatality in several months.[43] Paracetamol is the only medicine which has antidotum, N-Acetylcysteine (NAC). NAC is a beneficial therapy in DILI patients who develop progressively to fulminant liver failure. There is still no clinical evidence about corticosteroid and ursodeoxycholic acid as adjuvant therapy in DILI. The use of corticosteroid can be considered in DILI without improvement in 6-8 weeks and involving immune system.[44,50,51]

HEPATOCELLULER CELL CARCINOMA

Prevalence

The incidence and mortality rates of hepatoma achieves 65 million persons and 60.240 persons annually in Europe. In the United States, 21 million hepatoma cases and 18.400 fatality cases each year.[52] Liver cirrhosis in older people is more susceptible to develop to hepatoma than younger people. In western country, half cases of liver cirrhosis in older people (>60 years) develop to liver tumor and 40% of total cases develop progressively to hepatoma in aging 70 years old.[9] The mortality rates in older people account 60 cases per 100.000 men and 25 cases per 100.000 in people aging 80 – 84 years old.[53] Furthermore, liver disease in older people can develop to hepatoma without having fibrosis and cirrhosis previously.[9]

The Characteristics

Hepatoma characteristics of older people are different with younger people. In older people, hepatoma is mostly caused by hepatitis C whereas

chronic hepatitis B related to hepatoma mostly occurred in younger people.[54] Hepatitis B infection is mostly transmitted vertically from mother to child during antenatal care. Conversely, hepatitis C is often occurred in young adult. Thereefore, hepatoma patients who is infected by hepatitis B are 10 years younger than hepatoma caused by hepatitis C.[55] Not only are hepatitis B and C as main agents of hepatoma in old people, Non-Alcoholic Steato Hepatitis (NASH) is also one of the frequent agents causing hepatoma.[56] Liver fibrosis in older people living with hepatoma is milder than young people.[57]

Treatments

Currently, the treatment of hepatoma is still controversial. The first line treatment of hepatoma including surgery, Radiofrequency Ablation (RFA), Percutaneous Injection Therapy (PAIT), microwave ablation, and liver transplantation. There are also palliative treatments of hepatoma such as Transarterial Chemoembolization (TACE), transarterial radioembolization, targeted therapy, and dariotherapy.[54] According to several studies, the successful rate of hepatoma treatments in older people has poor outcomes. Surgical procedures can be applied in older people with liver tumor. Age is not an absolute contraindication in surgical procedures.[58] However, hepatoma patients with Clavien-Dindo grade 2 are more prone to surgical complications so that the close observation is necessary for them.[59] Radiofrequency ablation (RFA) is one of effective treatments in older people with hepatoma if the surgical procedures cannot be performed.[60] Tyrosine kinase inhibitors, sorafenib and lenvatinib, are most of targeted treatments used in hepatoma patients. Accroding to SHARP research in Asia-Pacific, sorafenib is safe to use in older people and has the same effectivity as younger people.[61,62] Multidisciplinary approaches are essential to optimize outcomes, yet treatment efficacy is inconsistent due to comorbidities and frailty.[63]

CONCLUSION

Aging induces significant morphological and functional changes in the liver, profoundly impacting disease progression and treatment outcomes in elderly populations. While advancements in antiviral therapies and diagnostic tools offer promising solutions, challenges remain in vaccine efficacy, management of drug-induced liver injury, and optimizing hepatocellular carcinoma treatments. Future research should focus on developing age-specific therapeutic protocols, Enhancing biomarkers for early detection, and investigating the role of multidisciplinary care in improving outcomes.

CONFLICT OF INTEREST

None.

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