

## DAFTAR PUSTAKA

- Acierno, C., Caturano, A., Pafundi, P.C., Nevola, R., Adinolfi, L.E., Sasso, F.C., 2020. Nonalcoholic fatty liver disease and type 2 diabetes: pathophysiological mechanisms shared between the two faces of the same coin. *Explor Med.*;1:287-306.
- Adinolfi, L. E., Restivo, L., Zampino, R., Guerrera, B., Lonardo, A., Ruggiero, L., et al., 2012. Chronic HCV infection is a risk of atherosclerosis. Role of HCV and HCV-related steatosis. *Atherosclerosis*. 221:496–502.
- Ajmera, V., Belt, P., Wilson, L.A., Gill, R.M., Loomba, R., Kleiner, D.E., et al., 2018. Among patients with nonalcoholic fatty liver disease, modest alcohol use is associated with less improvement in histologic steatosis and steatohepatitis. *Clin Gastroenterol Hepatol*. 16(1511–1520):e1515.
- Akahoshi M, Amasaki Y, Soda M, Tominaga T, Ichimaru S, Nakashima E, et al., 2001. Correlation between fatty liver and coronary risk factors: a population study of elderly men and women in Nagasaki, Japan. *Hypertens Res*. 24: 337-343
- Alves-Bezera, M., Cohen, D.E., 2019. Triglyceride metabolism in the liver. *Compr Physiol*. 8(1): 1–8.
- Ameer, F., Scandiuzzi, L., Hasnain, S., Kalbacher, H., Zaidi, N., 2014. De novo lipogenesis in health and disease. *Metabolism*. 63(7):895-902.
- Anantharaju, A., Feller, A., Chedid, A., 2002. Aging Liver. A review. *Gerontology*. 48: 343-353.
- Armstrong, M.J., Gaunt, P., Aithal, G.P., Barton, D., Hull, D., Parker, R., et al., 2016. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. *Lancet*. 387:679–690.
- Azzu, V., Vacca, M., Virtue, S., Allison, M., Vidal-Puig, A., 2020. Adipose tissue-liver cross talk in the control of whole-body metabolism: implications in nonalcoholic fatty liver disease. *Gastroenterology*.158:1899–912.
- Baiceanu, A., Mesdom, P., Lagouge M., Foulle F., 2016. Endoplasmic reticulum proteostasis in hepatic steatosis. *Nat Rev Endocrinol*. 12:710-22.
- Barb, D., Bril, F., Kalavalapalli, S., Cusi, K., 2019. Plasma fibroblast growth factor 21 is associated with severity of nonalcoholic steatohepatitis in patients with obesity and type 2 diabetes. *J Clin Endocrinol Metab*. 104:3327–36.
- Belfort, R., Harrison, S.A., Brown, K., Darland, C., Finch, J., Hardies, J., et al., 2016. A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis. *N Engl J Med*. 355:2297–2307.
- Bellentani S., 2017. The epidemiology of non-alcoholic fatty liver disease. *Liver Int*. 37(Suppl. 1):81–4.
- Beyer, I., Mets, T., Bautmans, I., 2012 Chronic low-grade inflammation and age-related sarcopenia. *Curr Opin Clin Nutr Metab Care*. 15: 12-22.
- Bradbury, M.W., 2006. Lipid metabolism and liver inflammation. I. Hepatic fatty acid uptake: possible role in steatosis. *Am. J Physiol*. 290: G194– G198.
- Bril, F., Portillo-Sanchez, P., Lomonaco, R., Orsak, B., Hecht, J., Tio, F., et al., 2017. Liver safety of statins in prediabetes or T2DM and nonalcoholic steatohepatitis: post hoc analysis of a randomized trial. *J Clin Endocrinol Metab*.102:2950–61.

- Browning, J.D., Horton, J.D., 2004. Molecular mediators of hepatic steatosis and liver injury. *J Clin Invest.* 114:147-52.
- Cassinotto, C., Boursier, J., de Ledinghen, V., Lebigot, J., Lapuyade, B., Cales, P., et al., 2016. Liver stiffness in nonalcoholic fatty liver disease: A comparison of supersonic shear imaging, FibroScan, and ARFI with liver biopsy. *Hepatology.* 63, 1817–1827.
- Cai, D., Yuan, M., Frantz, D. F , Melendez, P. A., Hansen, L., Lee, J., et al., 2005. Local and systemic insulin resistance resulting from hepatic activation of IKK-beta and NF-kappaB. *Nat Med.* 2005;11:183-90
- Carulli, L., Lonardo, A., Lombardini, S., Marchesini, G., Loria P., 2006. Gender, fatty liver and GGT. *Hepatology.* 44: 278-279
- Caussy, C., Soni, M., Cui, J., Bettencourt, R., Schork, N., Chen, C.H., et al., 2017. Nonalcoholic fatty liver disease with cirrhosis increases familial risk for advanced fibrosis. *J Clin Invest.*127:2697–704
- Chalasani, N., Younossi, Z., Lavine, J.E., Charlton, M., Cusi, K., Rinella, M., et al., 2018. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. *Hepatology.* 67:328-357.
- Chan, A. W., Wong, G.L., Chan H.Y., Tong, J.H., Yu, Y.H., Choi, P.C., Chan, H.L., et al., 2017. Concurrent fatty liver increases risk of hepatocellular carcinoma among patients with chronic hepatitis B. *J Gastroenterol Hepatol.* 32:667–676.
- Chap, M.A.L., 2019. Non Alcoholic Fatty Liver Disease CHAP. 23:28-34.
- Chakravarthy, M.V., Siddiqui, M.S., Forsgren, M.F., Sanyal, A.J., et al., 2020. Harnessing muscle–liver crosstalk to treat nonalcoholic steatohepatitis. *Front Endocrinol.* 11:592373.
- Charatcharoenwittaya, P., Pongpaibul, A., Kaosombatwattana, U., Bhanthumkomol, P., Bandidniyamanon, W., Pausawasdi, N., et al., 2017. The prevalence of steatohepatitis in chronic hepatitis B patients and its impact on disease severity and treatment response. *Liver Int.* 37:542–551.
- Cheng, Z., Ristow, M., 2013. Mitochondria and metabolic homeostasis. *Antioxid Redox Signal.* 19(3):240-242.
- Choi, H.S., Brouwer, W.P., Zanjir, W.M., de Man, R.A., Feld, J.J., Hansen BE, et al., 2020. Nonalcoholic steatohepatitis is associated with liver-related outcomes and all-cause mortality in chronic hepatitis B. *Hepatology.* 71:539–548.
- Cohen, D.E., and Fisher, E.A., 2013. Lipoprotein metabolism, dyslipidemia, and nonalcoholic fatty liver disease. *Semin Liver Dis.* 33: 380–388.
- Corey, K.E., Wilson, L.A., Altinbas, A., Yate,s K.P., Kleiner, D.E., Chung, R.T., et al., 2019. Relationship between resolution of non-alcoholic steatohepatitis and changes in lipoprotein sub-fractions: a post-hoc analysis of the PIVENS trial. *Aliment Pharmacol Ther.* 49:1205–13.
- Cusi, K., Orsak, B., Bril, F., Lomonaco, R., Hecht, J., Ortiz-Lopez, C., Tio, F., et al., 2016. Long-term pioglitazone treatment for patients with nonalcoholic steatohepatitis and prediabetes or type 2 diabetes melitus: a randomized trial. *Ann Intern Med.*165:305–315
- Dai, W., Ye, L., Liu, A., Wen, S.W., Deng, J., Wu, X., 2017. Prevalence of nonalcoholic fatty liver disease in patients with type 2 diabetes mellitus: A meta-analysis. *Med. (United States)* 96.

- de Lédinghen V, Vergniol J, Capdepon M, Chermak F, Hiriart JB, Cassinotto C, Merrouche W, Foucher J, Brigitte le B., 2014. Controlled attenuation parameter (CAP) for the diagnosis of steatosis: a prospective study of 5323 examinations. *J Hepatol*; 60: 1026-1031
- Diehl, A.M., Day, C., 2017. Cause, Pathogenesis, and Treatment of Nonalcoholic Steatohepatitis. *N. Engl. J. Med.* 377, 2063–2072.
- Di Mauro, S., Scamporrino, A., Filippello, A., Di Pino, A., Scicali, R., Malaguarnera, R., et al., 2021. Clinical and Molecular Biomarkers for Diagnosis and Staging of NAFLD. *Int. J. Mol. Sci.* 22, 11905.
- Dixon, J.B., Bhathal, P.S., O’Brien, P.E., 2001. Nonalcoholic fatty liver disease: Predictors of nonalcoholic steatohepatitis and liver fibrosis in the severely obese. *Gastroenterology* 121, 91–100.
- Donnelly, K.L., Smith, C.I., Schwarzenberg, S.J., Jessurun, J., Boldt, M.D., Parks, E.J., 2005. Sources of fatty acids stored in liver and secreted via lipoproteins in patients with nonalcoholic fatty liver disease. *J Clin Invest.* 115: 1343–1351.
- Eguchi, Y., Mizuta, T., Sumida, Y., Ishibashi, E., Kitajima, Y., Isoda, H., et al., 2011. The pathological role of visceral fat accumulation in steatosis, inflammation, and progression of nonalcoholic fatty liver disease. *J Gastroenterol.* 46 Suppl 1:70–8.
- Eguchi, Y., Hyogo, H., Ono, M., et al., 2012. Prevalence and associated metabolic factors of nonalcoholic fatty liver disease in the general population from 2009 to 2010 in Japan: a multicenter large retrospective study. *J Gastroenterol.*
- Eslam, M., Sanyal, A.J., George, J., 2020. International Consensus Panel. MAFLD: a consensus-driven proposed nomenclature for metabolic associated fatty liver disease. *Gastroenterology*.158:1999- 2014.e1.
- Eslam, M., Newsome, P.N., Sarin, S.K., Anstee, Q.M., Targher, G., RomeroGomez, M., et al., 2020. A new definition for metabolic dysfunction associated fatty liver disease: an international expert consensus statement. *J Hepatol.* 73:202-209.
- Eslam, M., Sarin, S.K., Wong, V.W.S., Fan, J.G., Kawaguchi, T., Ahn, et al., 2020. The Asian Pacific Association for the Study of the Liver clinical practice guidelines for the diagnosis and management of metabolic associated fatty liver disease. *Hepatology International*. Springer India.
- Filhoulaud, G., Guilmeau, S., Dentin, R., Girard, J., Postic C., 2013. Novel insights into ChREBP regulation and function. *Trends Endocrinol Metab* 24: 257–268.
- Friedrich-Rust, M., Hadji-Hosseini, H., Kriener, S., Herrmann, E., Sircar, I., Kau, A., et al., 2010. Transient elastography with a new probe for obese patients for non-invasive staging of nonalcoholic steatohepatitis. *Eur Radiol.* 20: 2390-239.
- Golabi, P., Paik, J., Reddy, R., Bugianesi, E., Trimble, G., Younossi, Z.M., et al., 2019. Prevalence and long-term outcomes of non-alcoholic fatty liver disease among elderly individuals from the United States. *BMC Gastroenterol.* 19(1):56.
- Greco, D., Kotronen, A., Westerbacka, J., Puig, O., Arkkila, P., Kiviluoto, T., et al., 2008. Gene expression in human NAFLD. *Am J Physiol Gastrointest Liver Physiol* 294: 1281–1287.
- Grefhorst, A., van de Peppel, I.P., Larsen, L.E., Jonker, J.W., Holleboom, A.G., 2021. The Role of Lipophagy in the Development and Treatment of Non-Alcoholic Fatty Liver Disease. *Front. Endocrinol.* 11:601627.

- Haeusler, R.A., McGraw, T.E., Accili, D., 2018. “Biochemical and cellular properties of insulin receptor signalling,” *Nature Reviews Molecular Cell Biology*. 19(1): 31–44.
- Hajiani, E., Alavinejad, P., Hashemi, S., Masjedizadeh, A., 2014. Comparison of the transient elastography (fibroscan) results among diabetic and non-diabetic patients with non- alcoholic fatty liver disease. *Gastroenterol. Hepatol*. 1, 00021.
- Hernández, L., The world ’ s leading publisher of Open Access books Built by scientists , for scientists TOP 1 % Nonalcoholic Fatty Liver Disease.
- Hirose, S., Matsumoto, K., Tatemichi, M., Tsuruya, K., Anzai, K., Arase, Y., et al., 2020. Nineteen-year prognosis in Japanese patients with biopsy-proven nonalcoholic fatty liver disease: lean versus overweight patients. *PLoS One*. 15:e0241770
- Imajo, K., Kessoku, T., Honda, Y., Tomeno, W., Ogawa, Y., Mawatari, H., et al., 2016. Magnetic Resonance Imaging More Accurately Classifies Steatosis and Fibrosis in Patients With Nonalcoholic Fatty Liver Disease Than Transient Elastography. *Gastroenterology*. 150: 626-637.
- Jian-Gao, F., Seung-Up, K., Vincent, W., 2017. New trends on obesity and NAFLD in Asia. *J. Hepatol*. 67, 862–873.
- Joo, E.J., Chang, Y., Yeom, J.S., Ryu, S., 2017. Hepatitis B virus infection and decreased risk of nonalcoholic fatty liver disease: a cohort study. *Hepatology*. 65:828–835.
- Juurinen, L., Tiikkainen, M., Haikkinen, A-M., Hakkarainen, A., Yki-Järvinen, H., 2006. Effects of insulin therapy on liver fat content and hepatic insulin sensitivity in patients with type 2 diabetes. *Am J Physiol Endocrinol Metab* 292: E829 –E835.
- Kawano, Y., Cohen, D.E., 2013. Mechanisms of hepatic triglyceride accumulation in non-alcoholic fatty liver disease. *J Gastroenterol*. 48: 434–441.
- Khoo, S., Wong, V.W.S., Goh, G.B.B., Fan, J., Chan, W.K., Seto, W.K., et al., 2020. Suboptimal treatment of dyslipidemia in patients with nonalcoholic fatty liver disease. *J Gastroenterol Hepatol* 2020;35:320–325.
- Kumar, M., Rastogi, A., Singh, T., Behari, C., Gupta, E., Garg, H., et al., 2013. Controlled attenuation parameter for noninvasive assessment of hepatic steatosis: does etiology affect performance? *J Gastroenterol Hepatol*. 28: 1194-1201
- Kwok, R., Choi, K.C., Wong, G.L., Zhang, Y., Chan, H.L., Luk, A.O., et al., 2017. Screening diabetic patients for non-alcoholic fatty liver disease with controlled attenuation parameter and liver stiffness measurements: a prospective cohort study. *Gut*. 65:1359–6.
- Kwok, R., Tse, Y.K., Wong, G.L., Ha, Y., Lee, A.U., Ngu, M.C., et al., 2014. Systematic review with meta-analysis: non-invasive assessment of non-alcoholic fatty liver disease--the role of transient elastography and plasma cytokeratin-18 fragments. *Aliment Pharmacol Ther*. 39: 254-269.
- Lai, L-L., Vethakkan, S.R., Mustapha, N.R.N., Mahadeva, S., Chan, W-K., 2020. Empaglifozin for the treatment of nonalcoholic steatohepatitis in patients with type 2 diabetes melitus. *Dig Dis Sci*. 65:623–631.
- Lambert, J.E., Ramos-Roman, M.A., Browning, J.D., Parks, E.J., 2014. Increased de novo lipogenesis is a distinct characteristic of individuals with nonalcoholic fatty liver disease. *Gastroenterology*. 146(3):726-735.

- Leite, N.C., Salles, G.F., Araujo, A.L.E., Villela-Nogueira, C.A., Cardoso, C.R.L., 2009. Prevalence and associated factors of non-alcoholic fatty liver disease in patients with type-2 diabetes melitus. *Liver Int.* 29(1):113–9.
- Li, Y., Huang, Y.S., Wang, Z.Z., Yang, Z.R., Sun, F., Zhan, S.Y., Liu, X.E., Zhuang, H., 2016. Systematic review with meta-analysis: The diagnostic accuracy of transient elastography for the staging of liver fibrosis in patients with chronic hepatitis B. *Aliment. Pharmacol. Ther.* 43, 458–469.
- Li, J., Zou, B., Yeo, Y.H., Feng, Y., Xie, X., Lee, D.H., et al., 2019. Prevalence, incidence, and outcome of non-alcoholic fatty liver disease in Asia, 1999–2019: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol* 2019;4:389–398.
- Lim, S., Kim, J.W., Targher, G., 2021. Links between metabolic syndrome and metabolic dysfunction-associated fatty liver disease. *Trends Endocrinol. Metab.* 32, 500–514.
- Lomonaco, R., Bril, F., Portillo-Sanchez, P., Ortiz-Lopez, C., Orsak, B., Biernacki, D., et al., 2016. Metabolic impact of nonalcoholic steatohepatitis in obese patients with type 2 diabetes. *Diabetes Care.* 39:632–8.
- Lonardo, A., Nascimbeni, F., Mantovani, A., Targher, G., 2018. Hypertension, diabetes, atherosclerosis and NASH: cause or consequence? *J Hepatol.* 68:335–2.
- Long, M.T., Nouredin, M., Lim, J.K., 2022. AGA Clinical Practice Update: diagnosis and management of nonalcoholic fatty liver disease in lean individuals: expert review. *Gastroenterology.* 163:764–74.
- Loomba, R., Abraham, M., Unalp, A., Lavine, J., Doo, E., Bass, N.M., et al., 2018. Nonalcoholic Steatohepatitis Clinical Research Network. Association between diabetes, family history of diabetes, and risk of nonalcoholic steatohepatitis and fibrosis. *Hepatology.* 56:943–51.
- Machado, M.V., Oliveira, A.G., Cortez-Pinto, H., 2011. Hepatic steatosis in hepatitis B virus infected patients: meta-analysis of risk factors and comparison with hepatitis C infected patients. *J Gastroenterol Hepatol.* 26:1361–1367
- Mantovani, A., Byrne, C.D., Bonora, E., Targher, G., 2018. Nonalcoholic fatty liver disease and risk of incident type 2 diabetes: a meta-analysis. *Diabetes Care.* 41:372–82.
- Marchesini, G., Brizi, M., Morselli-Labate, A.M., Bianchi, G., Bugianesi, E., McCullough, A.J., et al., 1999. Association of nonalcoholic fatty liver disease with insulin resistance. *Am J Med.* 107:450–5.
- Marchesini, G., Brizi, M., Bianchi, G., Tomassetti, S., Bugianesi, E., Lenzi, M., et al., 2011. Nonalcoholic fatty liver disease: a feature of the metabolic syndrome. *Diabetes* 150: 20.
- Masarone M., A. Federico, L. Abenavoli, C. Loguercio, and M. Persico, “Non alcoholic fatty liver: epidemiology and natural history,” *Reviews on Recent Clinical Trials*, vol. 9, no. 3, pp. 126–133, 2014
- Mehal, W.Z., 2013. The Gordian Knot of dysbiosis, obesity and NAFLD. *Nat Rev Gastroenterol Hepatol.* 10:637–44.
- Mikolasevic, I., Orlic, L., Franjic, N., Hauser, G., Stimac, D., Milic, S., 2016. Transient elastography (FibroScan® ) with controlled attenuation parameter in the assessment of liver steatosis and fibrosis in patients with nonalcoholic fatty liver disease - Where do we stand? *World J Gastroenterol.* 22(32): 7236–7251.
- Moller, D.E., 2011. Potential role of TNF-alpha in the pathogenesis of insulin resistance and type 2 diabetes. *Trends Endocrinol Metab.* 11:212–7.

- Moschen, A.R., Molnar, C., Enrich, B., Geiger, S., Ebenbichler, C.F., Tilg, H., 2011. Adipose and liver expression of interleukin (IL)-1 family members in morbid obesity and effects of weight loss. *Mol Med*.17:840-45
- Musso, G., Gambino, R., Cassader, M., Pagano, G., 2011. Meta-analysis: natural history of non-alcoholic fatty liver disease (NAFLD) and diagnostic accuracy of non-invasive tests for liver disease severity. *Ann Med*. 43:617-49.
- Nakajima, T., Nakashima, T., Yamaoka, J., Shibuya, A., Itoh, Y., Yoshikawa, T., 2012. Age is a negative, and visceral fat accumulation is a positive, contributor to hepatic steatosis, regardless of the fibrosis progression in Non-alcoholic Fatty Liver Disease. *J Gastroenterol Hepatol Res*.1: 315-319
- Nassir, F., Ibdah, J.A., 2014. Role of mitochondria in nonalcoholic fatty liver disease. *Int J Mol Sci*.15(5):8713-8742.
- Nassir, F., Rector, R.S., Hammoud, G.M., Ibdah, J.A., 2015. Pathogenesis and Prevention of Hepatic Steatosis. *Gastroenterol. Hepatol.* (N. Y). 11, 167–175.
- Olefsky, J.M., Glass, C.K., 2010. Macrophages, inflammation, and insulin resistance. *Annu Rev Physiol*. 72:219-46.
- Park, C.C., Nguyen, P., Hernandez, C., Bettencourt, R., Ramirez, K., Fortney, L., et al., 2017. Magnetic Resonance Elastography vs Transient Elastography in Detection of Fibrosis and Noninvasive Measurement of Steatosis in Patients With Biopsy-Proven Nonalcoholic Fatty Liver Disease. *Gastroenterology*. 152, 598–607.
- Patel, S., Siddiqui, M.B., Chandrakumaran, A., Rodriguez, V.A., Faridnia, M., Hernandez Roman, J., et al., 2021. Progression to cirrhosis leads to improvement in atherogenic milieu. *Dig Dis Sci*. 66:263–72.
- Peleg, N., Issachar, A., Arbib, O.S., Cohen-Naftaly, M., Braun, M., Leshno M, et al., 2019. Liver steatosis is a strong predictor of mortality and cancer in chronic hepatitis B regardless of viral load. *JHEP Rep*.1:9–16
- Perkumpulan Endokrinologi Indonesia (Perkeni), 2021. Pedoman Pengelolaan dan Pencegahan Diabetes Melitus Tipe 2 Dewasa di Indonesia.
- Polyzos, S.A., Mantzoros, C.S., 2015. Leptin in health and disease: facts and expectations at its twentieth anniversary. *Metabolism*. 64:5-12.
- Prashanth, M., Ganesh, H.K., Vimal M.V., John, M. , Bandgar T., 2021. Prevalence of nonalcoholic fatty liver disease in patients with type 2 diabetes melitus, *Journal of the Association of Physicians of India* . doi:10.1097/MD.00000000000008179.
- Rinella, M.E., Lominadze, Z., Loomba, R., Charlton, M., Neuschwander-Tetri, B.A., Caldwell, S.H., et al., 2017. Practice patterns in NAFLD and NASH: real life differs from published guidelines. *Therap Adv Gastroenterol*. 9:4–12
- Rinella, M.E., Neuschwander-Tetri, B.A., Siddiqui, M.S., Abdelmalek, M.F., Caldwell, S., Barb, et al., 2023. AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease, *Hepatology*.
- Robertson SA, Leininger GM, Myers MG Jr. Molecular and neural mediators of leptin action. *Physiol Behav*. 2008;94:637-42.
- Sanyal, D., Mukherjee, P., Raychaudhuri, M., Ghosh, S., Mukherjee, S., Chowdhury, S., 2015. Profile of liver enzymes in non-alcoholic fatty liver disease in patients with impaired glucose tolerance and newly detected untreated type 2 diabetes. *Indian J Endocr Metab*. 19:597-601.



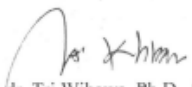

- Sanyal, A.J., Van Natta, M.L., Clark, J., Neuschwander-Tetri, B.A., Diehl, A., Dasarathy, S., et al., 2021. Prospective study of outcomes in adults with nonalcoholic fatty liver disease. *N Engl J Med.* 385:1559–69
- Samuel, V.T., Shulman, G.I., 2016. The pathogenesis of insulin resistance: integrating signaling pathways and substrate flux. *J Clin Invest* 126: 12–22.
- Sato, K., Goshio, M., Yamamoto, T., Kobayashi, Y., Ishii, N., Ohashi, T., et al., 2015. Vitamin E has a beneficial effect on nonalcoholic fatty liver disease: a meta-analysis of randomized controlled trials. *Nutrition.* 31:923–930.
- Schaffner, F., Thaler, H., 1986. Nonalcoholic fatty liver disease. *Prog Liver Dis.* 8:283-298.
- Shen, L.L., Liu, H., Peng, J., Gan, L., Lu, L., Zhang, Q., et al., 2011. Effects of farnesoid X receptor on the expression of the fatty acid synthetase and hepatic lipase. *Mol Biol Rep* 38: 553– 559, 2011.
- Siddiqui, M.S., Carbone, S., Vincent, R., Patel, S., Driscoll, C., Celi, F.S., et al., 2019. Prevalence and severity of nonalcoholic fatty liver disease among caregivers of patients with nonalcoholic fatty liver disease cirrhosis. *Clin Gastroenterol Hepatol.* 17:2132–3.
- Singh, S., Allen, A.M., Wang, Z., Prokop, L.J., Murad, M.H., Loomba, R., 2015. Fibrosis progression in nonalcoholic fatty liver vs nonalcoholic steatohepatitis: a systematic review and meta-analysis of paired biopsy studies. *Clin Gastroenterol Hepatol.* 13:643–54
- Sorbi, D., Boynton, J., Lindor, K.D., 1999. The ratio of aspartate aminotransferase to alanine aminotransferase: potential value in differentiating nonalcoholic steatohepatitis from alcoholic liver disease. *Am J Gastroenterol.* 94:1018-22.
- Sung, K.C., Kim, S.H., 2011. Interrelationship between fatty liver and insulin resistance in the development of type 2 diabetes. *J Clin Endocrinol Metab.* 96:1093-7.
- Tada, T., Kumada, T., Toyoda, H., Sone, Y., Takeshima, K., Ogawa, S., et al., 2018. Viral eradication reduces both liver stiffness and steatosis in patients with chronic hepatitis C virus infection who received direct-acting anti-viral therapy. *Aliment Pharmacol Ther.* 47:1012–1022.
- Tilg, H., Moschen, A.R., 2010. Evolution of inflammation in nonalcoholic fatty liver disease: the multiple parallel hits hypothesis. *Hepatology.* 52:1836-46
- Titchenell, P.M., Chu, Q., Monks, B.R., Birnbaum, M.J., 2015. Hepatic insulin signalling is dispensable for suppression of glucose output by insulin in vivo. *Nat Commun.* 6:7078.
- Tremaroli, V., Bäckhed, F., 2012. Functional interactions between the gut microbiota and host metabolism. *Nature.* 489:242-9.
- Tuong, T.T.K., Tran, D.K., Phu, P.Q.T., Hong, T.N.D., Dinh, T.C., Chu, D.T., 2020. Non-alcoholic fatty liver disease in patients with type 2 diabetes: Evaluation of hepatic fibrosis and steatosis using fibroscan. *Diagnostics.* 10(3):1–11.
- Ordoñez-Vázquez, A.L.; Juárez-Hernández, E.; ZuarthVázquez, J.M.; Ramos-Ostos, M.H.; Uribe, M.; Castro-Narro, G.; López-Méndez, I., 2022. Impact on Prevalence of the Application of NAFLD/MAFLD Criteria in Overweight and Normal Weight Patients. *Int. J. Environ. Res. Public Health*, 19, 12221.
- Unger, R.H., 2003. Lipid overload and overflow: metabolic trauma and the metabolic syndrome. *Trends Endocrinol Metab.* 14:398-403


- Vasconcellos, R., Alvarenga, E.C., Parreira, R.C., Lima, S.S., Resende, R.R., 2016. Exploring the cell signalling in hepatocyte differentiation. *Cell Signal* 28: 1773–1788.
- Vernon, G., Baranova, A., Younossi, Z.M., 2011. Systematic review: The epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. *Aliment Pharmacol Ther.* 34:274-85.
- Vilar-Gomez E., Calzadilla-Bertot, L., Wai-Sun, Wong, V., Castellanos, M., Aller-de la Fuente, R., et al., 2020. Type 2 diabetes and metformin use associate with outcomes of patients with non-alcoholic steatohepatitis-related, child-pugh a cirrhosis. *Clin Gastroenterol Hepatol*
- Welty, F.K., 2014. Hypobetalipoproteinemia and abetalipoproteinemia. *Curr Opin Lipidol.* 25(3):161-168.
- Wilder, J., Patel, K., 2014. The clinical utility of FibroScan((R) as a noninvasive diagnostic test for liver disease. *Med. Devices.* 7, 107–114.
- Williamson, R.M., Price, J.F., Glancy, S., Perry, E., Nee, L.D., Hayes, P.C., et al., 2011. Prevalence of and risk factors for hepatic steatosis and nonalcoholic fatty liver disease in people with type 2 diabetes: The Edinburgh type 2 diabetes study. *Diabetes Care.* 34(5):1139–44.
- Wong, V.W., Vergniol, J., Wong, G.L., Foucher, J., Chan, A.W., Chermak, F., et al., 2012. Liver stiffness measurement using XL probe in patients with nonalcoholic fatty liver disease. *Am J Gastroenterol.* 107: 1862-1871.
- Wong, R.J., Aguilar, M., Cheung, R., et al., 2015. “Nonalcoholic steatohepatitis is the second leading etiology of liver disease among adults awaiting liver transplantation in the United States. *Gastroenterology.* 148 (3) 547–555.
- World Health Organization , 2020. Training modules on hepatitis B and C screening, diagnosis and treatment. ISBN 978-92-9022-747-2.
- Xiao, G., Zhu, S., Xiao, X., Yan, L., Yang, J., Wu, G., 2017. Comparison of laboratory tests, ultrasound, or magnetic resonance elastography to detect fibrosis in patients with nonalcoholic fatty liver disease: A meta-analysis. *Hepatology.* 66, 1486–1501.
- Yang, Q., Vijayakumar, A., Kahn, B.B., 2018. “Metabolites as reglukosators of insulin sensitivity and metabolism,” *Nature Reviews Molecular Cell Biology.* 19 (10), 654.
- Ye, Q., Zou, B., Yeo, Y.H., Li, J., Huang, D.Q., Wu, Y., et al., 2020. Global prevalence, incidence, and outcomes of non-obese or lean non-alcoholic fatty liver disease: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol.* 5:739–52.
- Yilmaz, Y., Senates, E., Yesil, A., Ergelen, R., Colak, Y., 2014. Not only type 2 diabetes but also prediabetes is associated with portal inflammation and fibrosis in patients with non-alcoholic fatty liver disease. *J Diabetes Complications.* 28:328-31.
- Younes, R., Bugianesi, E., 2019. NASH in lean individuals. *Semin Liver Dis.* 39:86–95
- Younossi, Z.M., Koenig, A.B., Abdelatif, D., Fazel, Y., Henry, L., Wymer, M., 2016. Global epidemiology of nonalcoholic fatty liver disease—Meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology.* 64(1):73–84.
- Younossi, Z.M., McCullough, A.J., Ong, J.P., Barnes, D.S., Post, A., Tavill, A., et al., 2004. Obesity and non-alcoholic fatty liver disease in chronic hepatitis C. *J Clin Gastroenterol.* 38:705–709.
- Yu, S.J., Kim, W., Kim, D., Yoon, J.H., Lee, K., Kim, J.H., et al., 2015. Visceral obesity predicts significant fibrosis in patients with nonalcoholic fatty liver disease. *Medicine.* 94:e2159.

- Yan-Ci, Z., Guo-Jun, Z., Ze, C., Zhi-Gang, S., Jingjing, C., Hongliang, L., 2019. Nonalcoholic Fatty Liver Disease An Emerging Driver of Hypertension. *Hypertension*. 2020;75:275-284.
- Zhao, J.H., Cai, J.J., She, Z.G., Li, H.L., 2019. Noninvasive evaluation of nonalcoholic fatty liver disease: Current evidence and practice. *World J. Gastroenterol.* 25, 1307–1326.

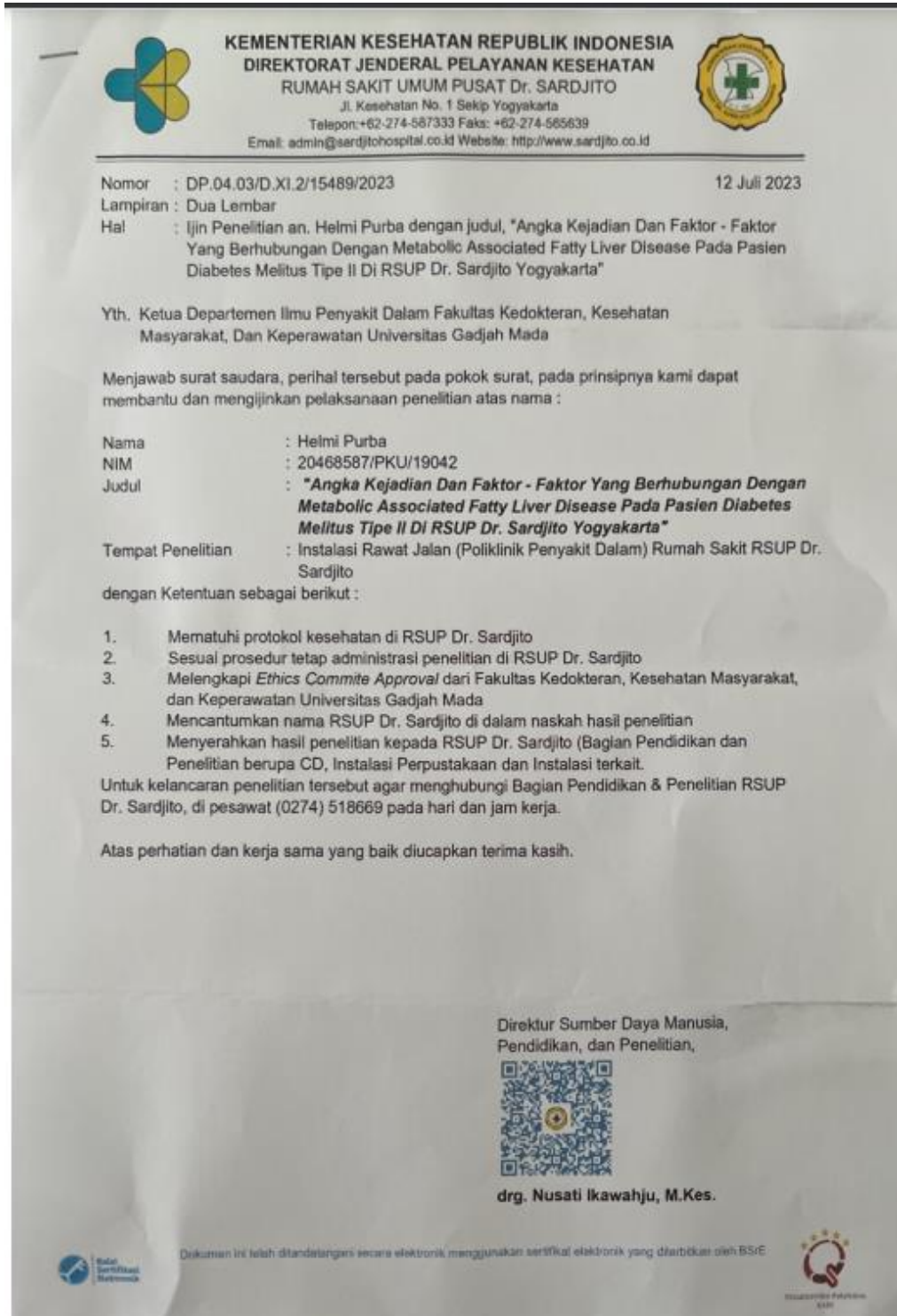
## LAMPIRAN

Lampiran 1. Persetujuan dari Komisi Etik Penelitian Kedokteran dan Kesehatan Fakultas Kedokteran Kesehatan Masyarakat dan Keperawatan Universitas Gadjah Mada

 <b>MEDICAL AND HEALTH RESEARCH ETHICS COMMITTEE (MHREC)</b> <b>FACULTY OF MEDICINE, PUBLIC HEALTH AND NURSING</b> <b>UNIVERSITAS GADJAH MADA – DR. SARDJITO GENERAL HOSPITAL</b> 	
<b>ETHICS COMMITTEE APPROVAL</b>	
Ref. No. : KE/FK/0997/EC/2023	
Title of the Research Protocol	: Angka Kejadian dan Faktor – Faktor yang Berhubungan dengan <i>Metabolic Associated Fatty Liver Disease</i> pada Pasien Diabetes Melitus Tipe II di RSUP Dr. Sardjito Yogyakarta
Document(s) Approved and version	: 1. Study protocol version 01 2023 2. Information for Subjects version 01 2023 3. Informed consent form version 01 2023
Principle Investigator	: Helmi Purba
Participating Investigator(s)	: 1. Dr. dr. Neneng Ratnasari, Sp.PD., K-GEH. 2. dr. R. Bowo Pramono, Sp.PD., K-EMD.
Date of Approval	: <b>21 JUN 2023</b> (Valid for one year beginning from the date of approval)
Institution(s)/place(s) of research	: Poliklinik Endokrin dan Poliklinik Gastroenterohepatologi Penyakit Dalam RSUP Dr. Sardjito Yogyakarta
The Medical and Health Research Ethics Committee (MHREC) states that the document above meets the ethical principle outlined in the International and National Guidelines on ethical standards and procedures for researches with human beings.	
The Medical and Health Research Ethics Committee (MHREC) has the right to monitor the research activities at any time.	
The investigator(s) is/are obliged to submit: <input checked="" type="checkbox"/> Progress report as a continuing review (state its due time) <input checked="" type="checkbox"/> Report of any serious adverse events (SAE) <input checked="" type="checkbox"/> Final report upon the completion of the study	
 Prof. dr. Tri Wibawa, Ph.D., Sp.MK(K). Panel's chairperson	 dr. Yana Supriatna, Sp.Rad(K), Ph.D. Panel's secretary
P.S: This letter uses signature scan of the panel's chairperson and Secretary of the Ethics Committee. The hardcopy official letter with authority's signature will be issued when it is possible and are kept as an archive of the Ethics Committee	
Validation number : 64939b7799756 ( <a href="http://komisietik.fk.ugm.ac.id/validasi">http://komisietik.fk.ugm.ac.id/validasi</a> )	



## Lampiran 2. Izin Penelitian dari RSUP Dr. Sardjito Yogyakarta



**KEMENTERIAN KESEHATAN REPUBLIK INDONESIA**  
**DIREKTORAT JENDERAL PELAYANAN KESEHATAN**  
**RUMAH SAKIT UMUM PUSAT Dr. SARDJITO**  
Jl. Kesehatan No. 1 Sekip Yogyakarta  
Telepon: +62-274-587333 Faks: +62-274-565639  
Email: [admin@sardjitohospital.co.id](mailto:admin@sardjitohospital.co.id) Website: <http://www.sardjito.co.id>

Nomor : DP.04.03/D.XI.2/15489/2023 12 Juli 2023  
Lampiran : Dua Lembar  
Hal : Ijin Penelitian an. Helmi Purba dengan judul, "Angka Kejadian Dan Faktor - Faktor Yang Berhubungan Dengan Metabolic Associated Fatty Liver Disease Pada Pasien Diabetes Melitus Tipe II Di RSUP Dr. Sardjito Yogyakarta"

Yth. Ketua Departemen Ilmu Penyakit Dalam Fakultas Kedokteran, Kesehatan Masyarakat, Dan Keperawatan Universitas Gadjah Mada

Menjawab surat saudara, perihal tersebut pada pokok surat, pada prinsipnya kami dapat membantu dan mengijinkan pelaksanaan penelitian atas nama :

Nama : Helmi Purba  
NIM : 20468587/PKU/19042  
Judul : **"Angka Kejadian Dan Faktor - Faktor Yang Berhubungan Dengan Metabolic Associated Fatty Liver Disease Pada Pasien Diabetes Melitus Tipe II Di RSUP Dr. Sardjito Yogyakarta"**

Tempat Penelitian : Instalasi Rawat Jalan (Poliklinik Penyakit Dalam) Rumah Sakit RSUP Dr. Sardjito


dengan Ketentuan sebagai berikut :

1. Mematuhi protokol kesehatan di RSUP Dr. Sardjito
2. Sesuai prosedur tetap administrasi penelitian di RSUP Dr. Sardjito
3. Melengkapi *Ethics Commite Approval* dari Fakultas Kedokteran, Kesehatan Masyarakat, dan Keperawatan Universitas Gadjah Mada
4. Mencantumkan nama RSUP Dr. Sardjito di dalam naskah hasil penelitian
5. Menyerahkan hasil penelitian kepada RSUP Dr. Sardjito (Bagian Pendidikan dan Penelitian berupa CD, Instalasi Perpustakaan dan Instalasi terkait.

Untuk kelancaran penelitian tersebut agar menghubungi Bagian Pendidikan & Penelitian RSUP Dr. Sardjito, di pesawat (0274) 518669 pada hari dan jam kerja.

Atas perhatian dan kerja sama yang baik diucapkan terima kasih.

Direktur Sumber Daya Manusia,  
Pendidikan, dan Penelitian,

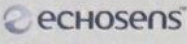






drg. Nusati Ikawahju, M.Kes.

Dokumen ini telah ditandatangani secara elektronik menggunakan sertifikat elektronik yang diterbitkan oleh BSR


### Lampiran 3. Prosedur Kerja Standar Fibroscan




1

	<h2 style="margin: 0;">PROSEDUR KERJA STANDAR</h2> <div style="border: 1px solid black; padding: 5px; text-align: center; margin: 5px auto; width: 80%;"> <b>FIBROSCAN 530 COMPACT</b> </div>	<div style="background-color: #0056b3; color: white; padding: 5px; display: inline-block;"> <b>Medquest</b> </div>
<b>I. DEFINISI</b>	Mesin Fibroscan 530 Compact digunakan untuk pemeriksaan stiffness dan CAP pada liver	
<b>II. ACUAN</b>	Fibroscan 530 Compact User Manual (English)	
<b>III. RINCIAN AKTIVITAS</b>	<p><u><b>RUNNING TEST</b></u></p> <ol style="list-style-type: none"> <li>1. Hubungkan instrumen ke sumber arus listrik,</li> <li>2. Hubungkan probe ke instrumen, lalu tekan tombol ON/OFF pada sisi kiri layar.</li> </ol> <div style="text-align: center; margin: 10px 0;">  </div> <ol style="list-style-type: none"> <li>3. Pilih icon  pada layar untuk memulai pemeriksaan.</li> </ol> <div style="text-align: center; margin: 10px 0;">  </div> <ol style="list-style-type: none"> <li>4. Masukkan data pasien dengan mengisi kolom informasi pasien. Setelah itu, tekan  untuk melakukan pemeriksaan.</li> </ol>	

Medquest

PT. Medquest Jaya Global  
Menara Salemba 6 th Fl Zone 1  
Jl. Salemba Raya No. 5 - 5A  
Jakarta Pusat 10440 - Indonesia  
+62-21 39842961 +62-21 31937736


Scanned with CamScanner

5. Jika dalam 1 hari terdapat lebih dari 1 pasien, maka input terlebih dahulu data pasien dengan menekan icon . Untuk melihat data pasien yang telah diinput tekan icon . Setelah memilih pasien yang akan diperiksa, tekan icon .

6. Setelah selesai pemeriksaan, tekan  untuk menghentikan pemeriksaan.

7. Bersihkan probe dari gel dan letakkan kembali ke probe holder.



9. Print hasil pemeriksaan.

10. Untuk mematikan alat, tekan tombol ON/OFF pada sisi kiri layar dan tekan tombol power ke posisi 0.

#### TEKNIK PEMERIKSAAN

1. Pengukuran dilakukan pada lobus hati bagian kanan diantara tulang rusuk.
2. Pasien berbaring telentang dengan lengan kanan dalam posisi abduksi maksimal.



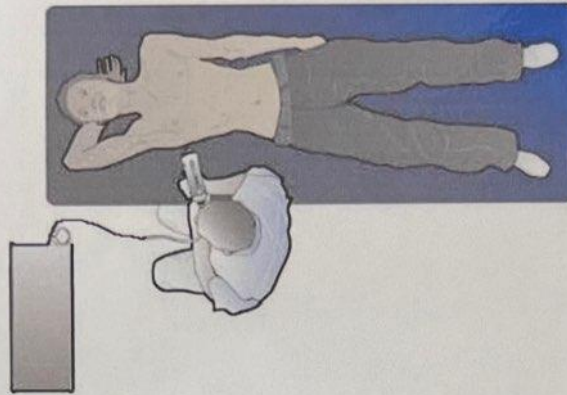
3. Operator duduk di sisi kanan pasien, menghadap ke dada pasien dan layar monitor.
4. Lengan kanan bersandar pada tempat tidur di sepanjang dada pasien.
5. Keseluruhan berat probe harus bertumpu pada tangan kanan.

**Medquest**

PT. Medquest Jaya Global  
Menara Salemba 6 th Fl Zone 1  
Jl. Salemba Raya No. 5 - 5A  
Jakarta Pusat 10440 - Indonesia  
+62-21 39842961 +62-21 31937736

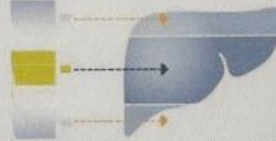
CS Scanned with

6. Tangan kiri membantu menjaga agar *probe* senantiasa berada di posisi yang tepat.



7. Selalu perhatikan probe, antara lain:

7.1 Posisi probe diantara tulang iga.



7.2 Posisi probe harus tegak lurus terhadap permukaan kulit.



7.3 Indikator tekanan pada level hijau.

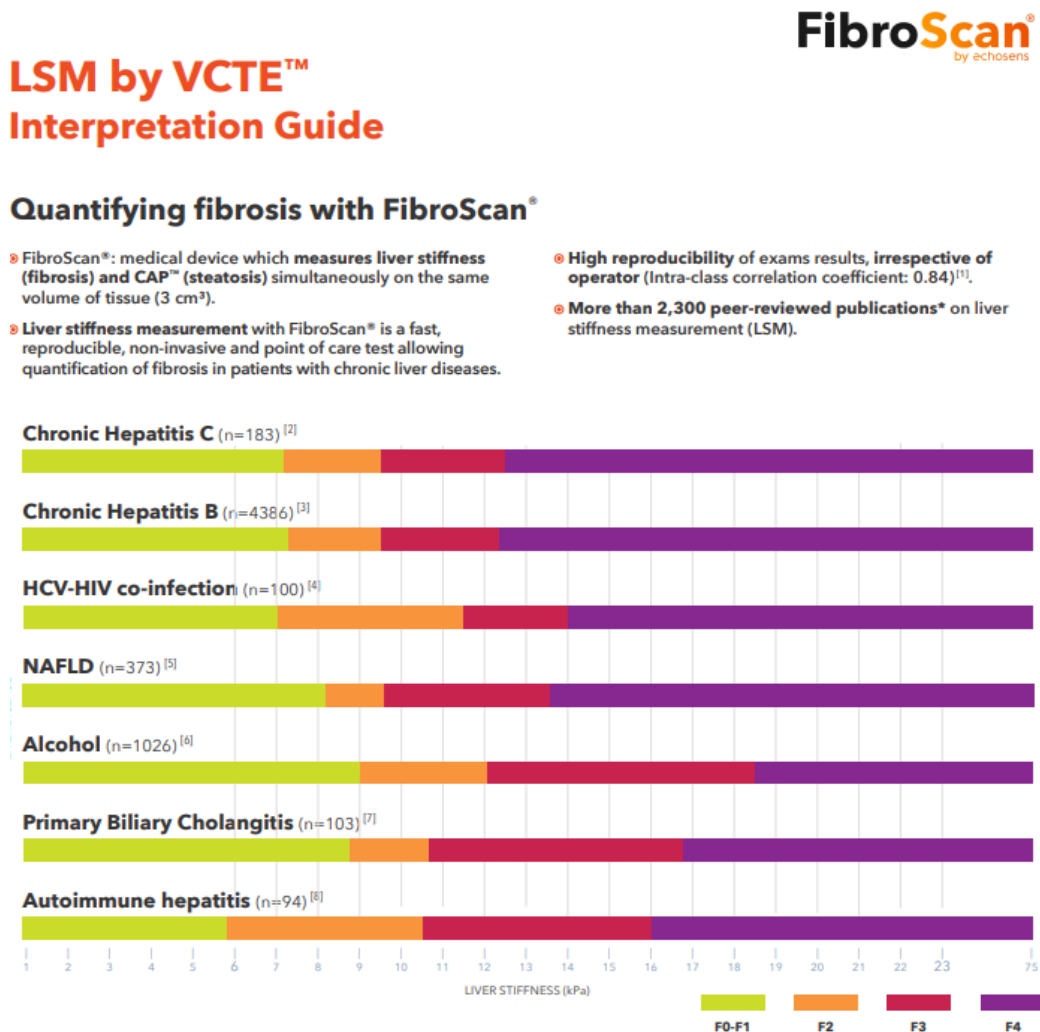


Medquest

PT. Medquest Jaya Global  
Menara Salemba 6 th Fl Zone 1  
Jl. Salemba Raya No. 5 - 5A  
Jakarta Pusat 10440 - Indonesia  
+62-21 39842961 +62-21 31937736

CS Scanned with

#### Lampiran 4. Panduan Interpretasi Derajat Fibrosis Hati (Li *et al.*, 2016)



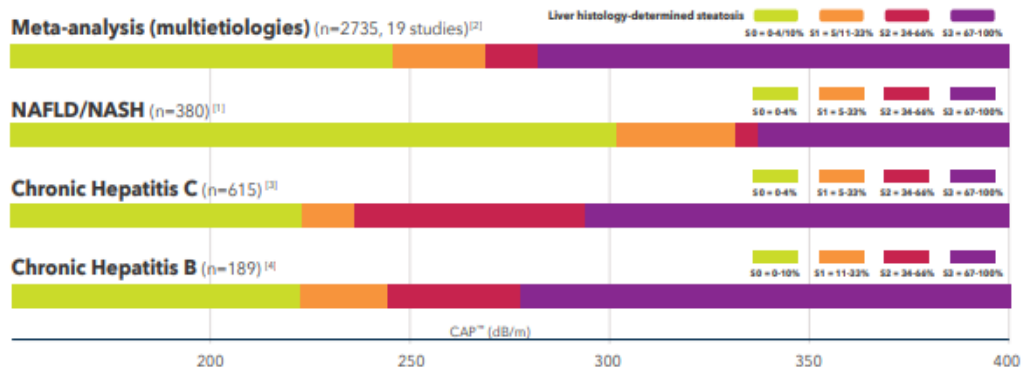
## Lampiran 5. Panduan interpretasi derajat steatosis hati (Li *et al.*, 2016)

### CAP™ Interpretation Guide

**FibroScan®**  
by echosens

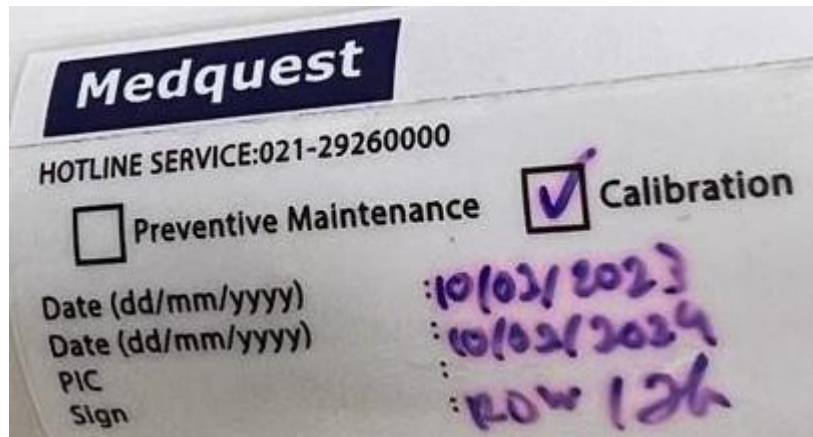
#### Quantifying steatosis with FibroScan®

- CAP™ measurement with FibroScan® is a fast, reproducible, non-invasive and point of care test allowing quantification of steatosis in patients with NAFLD and other fatty liver diseases.
- The existing literature demonstrates that CAP™ values correlate with the amount of steatosis<sup>[2]</sup>.
- Early detection of minimal hepatic steatosis: from 5% onwards (Ultrasound allows to detect from 30% only).
- Valuable insights for patient monitoring during therapy, intervention or lifestyle change<sup>[3,4]</sup>.
- CAP™ not influenced by fibrosis and inflammation<sup>[1]</sup>.



## Lampiran 6. Kalibrasi Fibroscan

Fibroscan telah dikalibrasi tanggal 10 Maret 2023 dan berlaku sampai tanggal 10 Februari 2034.



## Lampiran 7. Nilai Koefisien dan Nilai Eksponensial (Odds Rasio)

**Tabel 2.2** Nilai Koefisien dan Nilai Eksponensial (Odds Rasio)

Beta	EXP(Beta) = Odds Rasio	Beta	EXP(Beta) = Odds Rasio
-1,00	0,37	0,00	1,00
-0,90	0,41	0,10	1,11
-0,80	0,45	0,20	1,22
-0,70	0,50	0,30	1,35
-0,60	0,55	0,40	1,49
-0,50	0,61	0,50	1,65
-0,40	0,67	0,60	1,82
-0,30	0,74	0,70	2,01
-0,20	0,82	0,80	2,23
-0,10	0,90	0,90	2,46
0,00	1,00	1,00	2,72