NECA-Health Technology Reassessment Project

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Health Technology Reassessment Report 2020

Serum Liver Fibrosis Test

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Summary Statement

Background

Serum liver fibrosis test is a blood test to assess liver fibrosis, expect prognosis and assess treatment effect in patient with signs or symptoms of chronic liver diseases. This test is a medical technology publicly announced (a Ministry of Health and Administration Announcement #2014-195 (Oct. 31, 2014) as a non-payment item after the New Medical Technology Assessment in 2013.

Serum liver fibrosis test was assessed as safe and effective by assisting invasive liver biopsy when used to assess liver fibrosis, expect prognosis and assess treatment effect through New Medical Technology Assessment in 2013

As a result of internal monitoring, it was decided that the technology - serum liver fibrosis test - be re-assessed for safety and effectiveness. Therefore, the technology was brought to the 1st Health Technology Reassessment Committee in 2020 for re-assessment, in an attempt to find the ground of efficient use of health and medical resources.

Comprised of 6 different sub-committee members (2 gastroenterologists (specialized in liver diseases), 2 laboratory doctors, 1 radiologist, 1 evidence-based medicine specialist), the sub-committee for re-assessment of the technology (the “sub-committee”) held four different review meetings starting August 2020 and ended January 2021. Results of such re-assessment and the final recommendation grade was determined in the 3rd Health Technology Reassessment Committee in 2021 (Mar. 12, 2021).

Methodology

Systematic review was performed to re-assess the clinical safety and effectiveness of the technology - serum liver fibrosis test - in assessment of liver fibrosis and expectation of prognosis in patient with suspected chronic liver disease or confirmed patient with chronic liver disease.

Three different international databases and five different domestic databases were used to select studies. Selection of studies based on the inclusion and exclusion criteria, and performed by two reviewers independently. The selected studies were screened by the sub-committee for confirmation.

These two separate reviewers reached a consensus in that they perform risk of bias assessment on a separate basis, using QUADAS-2. The collected data were meta-analyzed since they were adequate for quantitative analysis.

The Health Technology Reassessment Committee determined recommendation grade for the technology based on the discussions underwent by the sub-committee.

Result

A total of 44 studies (including 16 studies from the previous New Medical Technology Assessment in 2013) were systematically reviewed for assessment of safety and effectiveness of serum liver fibrosis test.

Safety

Safety of serum liver fibrosis test was assessed in terms of test-related complication, delay in treatment due to false negative result, and over-diagnosis due to false positive result.

The technology is a blood test where sampling of specimen out of the sampled blood is conducted in *in vitro* settings. Neither test-related safety nor safety-related complication was reported. Therefore, the technology was assessed safe. None of the selected studies reported delayed treatment or over-diagnosis in relation to the test results.

Efficacy

Efficacy of this technology was assessed in terms of i) diagnostic accuracy (assessment of liver fibrosis and expectation of prognosis) and ii) impact on medical results (decrease in side effects related to decreased liver biopsy needs, improvement in quality of life, extended survival). The purpose of the technology includes, under the Public Announcement, assessment of treatment effect. With liver fibrosis assessment covers assessment of therapeutic effect of anti-virus agent, this study replaces assessment of treatment effect with diagnostic accuracy.

Out of all selected studies, 25 reported diagnostic accuracy on liver fibrosis assessment in the technology. AUC for the technology, varying by stage of liver fibrosis, was 0.61 for statistically significant liver fibrosis (F≥2), 0.88 for progressed liver fibrosis (F≥3) and 0.85 for liver cirrhosis (F=4). Therefore, it can be said that AUC was higher in cases with progressed liver fibrosis or liver cirrhosis.

Out of all selected studies, 17 reported diagnostic accuracy of liver fibrosis scan (FibroScan) compared to the technology. AUC for FibroScan, also varying by stage of liver fibrosis, was 0.86 for statistically significant liver fibrosis (F≥2), 0.91 for progressed liver fibrosis (F≥3) and 0.93 for liver cirrhosis (F=4). Therefore, it can also be said that AUC was slightly higher in cases with progressed liver fibrosis or liver cirrhosis.

A total of 9 studies reported the prognosis result of serum liver fibrosis, and the average follow-up period was 2.7-11.2 years. Out of those 9 studies, 6 implied statistically significant inter-Group difference between High Serum Liver Fibrosis Result Group and Low Serum Liver Fibrosis Result Group. It was also reported in those 6 studies that bad prognosis such as liver-related problems (hepatocellular carcinoma, esophageal varix, ascites, etc.) in patients with liver cirrhosis (F=4), who had high serum liver fibrosis result.

There was only 1 study reporting event-free survival rate at Year 10 and Year 20 on the follow-up, where survival rate was lower when serum liver fibrosis result was high.

Impact of the technology on medical result was assessed by decrease in side effects related to decreased liver biopsy needs, improvement in quality of life and extended survival. None of the selected studies reported decrease in side effects related to decrease of liver biopsy needs. Out of all selected studies, 5 reported decrease in liver biopsy needs by 48% to 86%. None of the selected studies reported quality of life and extended survival.

With the above being said, the sub-committee decided that use of the technology - serum liver fibrosis test - in patient with suspected chronic liver disease or confirmed patient with chronic liver disease - has clinical benefit since its impact on medical results in relation to diagnostic accuracy and decrease in liver biopsy needs is tolerable.

Economic Feasibility

Only 1 study (Soto et al. 2017) reported the technology's economic impact, where use of annual serum liver fibrosis test in combination with radiographic liver stiffness measurement and annual serum liver fibrosis test without any combination was analyzed to prevent the average of 12.9 deaths and 13.3 deaths per 100 population from taking place in patient with hepatitis C and incremental cost-effectiveness ratios(ICER) per quality-adjuster life year(QALY) were €13,400 and €11,500, respectively. In patient with alcoholic liver diseases, use of annual serum liver fibrosis test in combination with radiographic liver stiffness measurement and annual serum liver fibrosis test without any combination was analyzed to prevent the average of 11.7 deaths and 22.1 and ICER per QALY were €280 and €190, respectively.

Conclusion and Suggestion

The sub-committee suggests, based on the selected studies, as follows:

Serum liver fibrosis test is a safe and effective invasive means of assisting liver biopsy when used to assess liver fibrosis, expect prognosis and assess treatment effect in patient with suspected chronic liver disease or confirmed patient with chronic liver disease, regardless of stage of liver fibrosis (statistically significant liver fibrosis (F≥2), progressed liver fibrosis (F≥3), liver cirrhosis (F=4)).

In the 3rd Health Technology Reassessment Committee in 2021 (Mar. 12, 2021), the technology as a blood test where sampling of specimen out of the sampled blood is conducted in *in vitro* settings was determined safe with no test-related safety affected and none of studies reporting delay in treatment due to false negative results or over-diagnosis due to false positive results. Appreciating the technology's greater accessibility compared to any invasive means of liver biopsy, the Health Technology Reassessment Committee recommended (Recommendation Grade I-b) use of the technology for assessment of progression of fibrosis and expectation of prognosis in patient with suspected chronic liver disease or confirmed patient with chronic liver disease, regardless of stage of liver fibrosis (statistically significant liver fibrosis, progressed liver fibrosis, liver cirrhosis).

Keywords

Enhance Liver Fibrosis (ELF), Chronic liver diseases, Liver fibrosis