Systematic Review and/or Meta-Analysis Rationale

1. **Comment:** The rationale for conducting the systematic review / meta-analysis.
Chronic liver disease is a progressive degeneration of liver functions for more than six months. The prevalence of the chronic liver disease is increasing with the aging of the population, excessive drinking, and obesity. In recent years, new cases of chronic hepatitis B, chronic hepatitis C, primary biliary cholangitis, and nonalcoholic fatty liver disease (NAFLD) have been constantly reported. Chronic hepatitis is a common disease induced by viral infection, which manifests as inflammation/necrosis of hepatocytes. The repeated regeneration of these cells will lead to liver fibrosis. Patients with liver fibrosis often suffer from portal hypertension and hepatocellular carcinoma (HCC), which may increase their risk of mortality. Therefore, early identification and specific immunotherapy of patients with liver fibrosis or liver cirrhosis are critical, which may regress liver fibrosis and liver cirrhosis, thereby preventing progression and decompensation. Accordingly, identifying the fibrosis stage in patients with chronic liver disease is of great importance.

2. **Comment:** The contribution that it makes to knowledge in light of previously published related reports, including other meta-analyses and systematic reviews.
To our knowledge, there is no systematic review assessing the accuracy of M2BPGi in the diagnosis of the stage of liver fibrosis. This study is the first systematic review that focuses on this topic. A total of 24 trials with 3,039 patients were included in this meta-analysis. The meta-analysis results revealed that the AUC values for fibrosis stages ≥1, ≥2, ≥3, and ≥4 were 0.69, 0.76, 0.86, and 0.87, respectively. This suggests that M2BPGi has the best diagnostic performance for fibrosis stage ≥4. M2BPGi is relatively reliable in the prediction of the stage of liver fibrosis and can provide patients with a noninvasive, accurate, and acceptable method for monitoring the stage of fibrosis. However, large-scale clinical studies are needed to be conducted in multiple countries to validate our findings.