**IV .Discussion**

Singh *et al.* [1] conducted a meta-analysis to evaluate the annual progression rate of fibrosis and found 11 cohort studies enrolling 411 patients with documented liver biopsies grouped into 150 patients with evidence of NAFLD and 261 patients with evidence of NASH. The time interval between the first and the second biopsy was at least one year. A pooled-weighted annual fibrosis progression rate was calculated. Initially, the distribution of fibrosis for stages F0, F1, F2, F3 and F4 was 35.8%, 32.5%, 16.7 %, 9.3% and 5.7% respectively, and over 2145.5 person-years of follow-up evaluation, 33.6% had fibrosis progression, 43.1% had stable fibrosis, and 22.3% had an improvement in fibrosis stage. The annual fibrosis progression rate in patients with NAFL who had stage F0 fibrosis at baseline was 0.07 stages compared with 0.14 stages in patients with NASH. These findings correspond to 1 stage of progression over 14.3 years for patients with NAFL and 7.1 years for patients with NASH.

Ratziu *et al*.[2] conducted a study on 93 patients with abnormal liver function tests and BMI > 25 kg/m2 . 34 patients had no fibrosis, 31 had F1 fibrosis (portal tracts) and 28 had septal fibrosis (F2-F4). 20 patients had < 10% steatotic hepatocytes and 48 patients had ≥ 40 % steatotic hepatocytes. Of the 28 patients with septal fibrosis, all except 1 had necroinflammatory activity, steatosis were present in all except 2 and massive steatosis were present in 20 patients. The 31 patients with F1 fibrosis, 12 had necroinflammatory activity while 3 patients had this F1 as isolated finding with no other histological findings. The 34 patients with F0, 10 patients has no other findings ( i.e. normal liver biopsy), 15 patients showed steatosis alone, 9 patients showed steatosis with necroinflammation without fibrosis. That is to say, 30% of patients who are overweight and with abnormal liver function tests had septal fibrosis (F2-F4) and 11% had cirrhosis (F4). Grouping the variables into 2 groups revealed that the variables associated with high significant correlation with this septal fibrosis were: age ≥ 50 year, BMI ≥ 28, presence of diabetes, serum triglyceride levels ≥ 1.7 mmol/dL, GGT enzyme ≥ 4 times upper level of normal, presence of necroinflammation on biopsy whether piecemeal or lobular necrosis, and massive steatosis. Whereas, using step-by-step logistic regression for the variables revealed that the only significant and correlated variables with septal fibrosis at time of doing the biopsy were age ≥ 50 year, BMI ≥ 28, serum triglyceride levels ≥ 1.7, and ALT ≥ 2 times upper time of normal explaining 30% of variability of septal fibrosis. The significant variables found in the biopsy findings and correlated with septal fibrosis were only necroinflammatory activity, but the massive steatosis, Mallory bodies and/or polymorphnuclear infiltrate, and total iron score> 3 were not statistically significant. Doing the step-by-step logistic regression combining the 4 continuous variables and the necroinflammatory activity, the only variables with statistical significance were the age ≥ 50 year, BMI ≥ 28, and the necroinflammatory activity explaining 35% of variability of septal fibrosis. Ratziu *et al.* [2] designed a BAAT score which is the sum of the 4 categorical variables: BMI (≥ 28 =1, < 28 =0), age at liver biopsy(≥50=1,<50=0), ALT(≥2N=1, <2N=0), serum triglyceride(≥1.7 mmol/dL=1, <1.7=0) to predict the septal fibrosis. BAAT score of 0 or 1 was present in 30%, all of them had no septal fibrosis. BAAT score of 4 was present in 4 patients; all of them had septal fibrosis. The 0 or 1 score had 100% sensitivity, 47% specificity, 45% positive predictive value, and 100% negative predictive value. The 4 score had 14% sensitivity, 100% specificity, 100% positive predictive value, and 73% negative predictive value. The second liver biopsy was performed in 14 patients with a median follow up period of 5 years (range=1.5-15years) to figure out possible fibrosis progression. They had F0 (4 patients) and F1 (10 patients) at initial liver biopsy. All were still over weight with BMI ≥ 25 and all had abnormal liver function tests at the time of second liver biopsy. Four patients with initially F0 and no necroinflammatory activity remained stable in F0 with no activity at the follow up biopsies. Another 4 patients with initially F1 and no necroinflammatory activity regressed to F0 with no activity at the follow up biopsies. Two patients with initially F1 and no necroinflammatory activity remained stable in F1 with no activity at the follow up biopsies. Another two patients with initially F1 and necroinflammatory activity remained stable in F1 with activity at the follow up biopsies. One patient with initially F1 and necroinflammatory activity progressed to F2 with activity at the 5.5 year follow up biospy. Another one patient with initially F1 and necroinflammatory activity progressed to F4 with activity at the 5 year follow up biopsy.

References

[1] S. Singh, A. M. Allen, Z. Wang, L. J. Prokop, M. H. Murad, and R. Loomba, “Fibrosis progression in nonalcoholic fatty liver vs nonalcoholic steatohepatitis: a systematic review and meta-analysis of paired-biopsy studies,” *Clin. Gastroenterol. Hepatol.*, vol. 13, no. 4, pp. 643–654, 2015.

 [2] V. Ratziu *et al.*, “Liver fibrosis in overweight patients,” *Gastroenterology*, vol. 118, no. 6, pp. 1117–1123, 2000.