Assays for serum levels of liver enzymes, including aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma glutamyl transpeptidase, are the most common laboratory tests for the detection of liver disease. These enzyme levels can be used as markers of liver parenchymal injury or biliary tract disorders. A dramatic increase of serum AST or ALT is commonly observed in acute liver damage such as viral hepatitis, toxic hepatitis, and alcoholic liver disease. However, recent studies suggest that serum ALT level may be an indicator of overall health or a predictor of future mortality. Blood ALT level follows a continuous distribution rather than discrete, thus cut-off concentration that discriminates between those with healthy and diseased livers is not clearly defined. The upper normal limit for serum ALT has previously been calculated from a supposedly healthy reference population, yet, in most cases, the reference population probably included people with mild to moderate liver diseases. Consequently, using the conventional normal range can lead to an underestimated prevalence of health problems, which may be linked to a moderate elevation of AST. There is little information on the relationship between ALT level of normal to near normal range and subsequent mortality and morbidity. The significance of mild to moderate increase in serum ALT is not fully understood especially among apparently healthy individuals.

In order to understand the full spectrum of ALT levels in relation to liver disease and overall health, long-term prospective investigations are required. The Korea Medical Insurance Corporation (KMIC) study, a prospective cohort study based on the national health insurance program in Korea, addressed this issue. In this study, there were 142,055 individuals aged 35-59 years in whom baseline demographic and laboratory data obtained between 1990 and 1992 is available. This cohort was followed up to 2000, when death certificates were used to determine survival and causes of death. At baseline, 9.0% of men and 1.6% of women had serum ALT \( \geq 40 \) U/L. Higher serum ALT levels were correlated with higher mortality from all causes and liver disease. As expected, the effect of ALT was much larger on liver-specific mortality. For example, compared to those with ALT < 20 U/L, men with ALT \( \geq 100 \) U/L had 59 times the risk of liver disease mortality. Even within normal range higher ALT levels were associated with increased liver disease mortality. People with ALT 20-29 U/L had significantly higher liver disease mortality than those with ALT < 20 U/L; adjusted hazard ratios were 2.9 (95% CI 2.4 to 3.5) in men and 3.8 (95% CI 1.9 to 7.7) in women. A similar study was performed in a US population. ALT levels were abstracted from a community-wide laboratory database for 6,823 adult residents of Olmsted County, Minnesota in 1995. Of those, 5,912 had results within normal limits and 911 (13.4%) were abnormal. ALT level between 1 and 2 times the upper normal limit were associated with a standardized mortality ratio (SMR) of 1.21 (\( P = 0.23 \)), whereas ALT level greater than 2 times the upper normal limit had an SMR of 1.51 (\( P = 0.02 \)).

Serum ALT level is also associated with cardiovascular disease morbidity and mortality. In the KMIC study, ALT level was correlated to the risk of cardiovascular mortality. Men with an ALT \( \geq 100 \) U/L had a 2.9 (95% CI, 1.5 to 5.6)
times higher risk of cardiovascular mortality when compared to those with ALT < 20 U/L.2 In a different investigation of the KMIC cohort, serum ALT level was associated specifically with hemorrhagic stroke incidence.12 Other East Asian studies have reported that ALT elevation or liver dysfunction is associated with cardiovascular risk factors6,7,13 and subclinical atherosclerosis.14,15 Serum ALT level has been evaluated as a marker of cardiovascular health also in the general US population. A cross-sectional study assessed the association between elevated ALT activity (> 43 IU/L) and the future risk of coronary heart disease (estimated by Framingham Risk Score (FRS)), using the datasets from the Third National Health and Nutrition Examination Survey. Among participants without viral hepatitis or excessive alcohol consumption, those with elevated ALT activity (n=267) had a higher FRS than those with normal ALT activity (n=7259) in men (hazard ratio for CHD 1.28, 95% CI 1.07-1.5) and women (hazard ratio for CHD 2.14, 95% CI 1.5-3.0). However, elevated ALT activity was not associated with higher FRS among nonobese participants with viral hepatitis or excessive alcohol consumption.16 These findings suggest that elevated serum ALT activity in the absence of viral hepatitis or excessive alcohol consumption is associated with increased cardiovascular risk and the association is mostly due to nonalcoholic fatty liver disease (NAFLD). Elevated ALT level is also closely related to major cardiovascular risk factors and the metabolic syndrome. Epidemiologic studies have reported associations between ALT elevation and the metabolic syndrome in a general adult population,7 obese people,26,27 elderly men,28 postmenopausal women,29 and even adolescents.30 Moreover, the association was observed even in the normal to near normal range of ALT in a dose-related manner.7 The most probable explanation for the association between serum ALT level and cardiovascular disease or metabolic syndrome is NAFLD. NAFLD is the most common and increasing cause of unexplained ALT elevations in Western populations and in some Asian populations.2,31 A growing body of evidence supports an association between NAFLD and the metabolic syndrome.3,7,10-14,30-35 Recent studies have added evidence that insulin resistance is a key component of the metabolic syndrome and also contributes to the development of NAFLD.7,13,36,37 Other possible biological mechanisms linking ALT elevation and cardiovascular disease may include, oxidative stress, inflammation, abnormal coagulation, co-existing disease, and medications.9,12,17-22

In summary, serum ALT level is frequently measured as a part of a liver function test, but the significance of ALT test may be underestimated especially among apparently healthy individuals. ALT tests have many advantages as a screening tool for the general population, since it is minimally invasive, inexpensive, and a highly sensitive marker of liver disease and general health, however, additional data are needed to determine optimal cutoff levels and schedules for ALT screening as well as to assess the practicability and cost-effectiveness.

References