Background: Himachal Pradesh is a hill state in North India in the Western Himalayas. β-thalassemia is a genetic disorder of hemoglobin inherited in an autosomal recessive manner that results in defective globin production leading to the early destruction of red blood cells. β-thalassemia has long been neglected in Himachal Pradesh due to popular belief that it runs along "Lahore-Gujarat-Punjab" belt in India. Therefore, there is no β-thalassemia testing facility currently in the state. Methods: To estimate the prevalence of β-thalassemia carriers, we calculated the sample size based on probability proportional to size self-weighing design. In each of 20 selected colleges, 111 students having an age of 18–25 were tested for high-performance liquid chromatography (HPLC) and complete blood count. Some were further tested for the mutations. We computed sensitivity, specificity, positive predictive value (PPV) and negative predictive value, and receiver operating characteristic curve for mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH) red cell parameters. Results: Of the 2220 students, 57 were found to be β-thalassemia carrier by HPLC. The overall prevalence rate was 2.6% which translates to probable 180,000 β-thalassemia carriers in Himachal Pradesh. Six districts bordering highly endemic Punjab had a higher prevalence. Hemoglobin D-Punjab, Heterozygous-Iran Trait, and raised fetal hemoglobin were found. Thalassemia major and sickle cell disease were not found. Anemic status or MCV/MCH parameters were not found to be reliable predictors of thalassemia carrier status among the healthy populations of HP. The predominant mutation found was IVS 1–5 G > C. Conclusion: Popular ongoing strategy for screening with MCV and MCH has low-PPV and can miss upto 37% of true thalassemia carriers. HPLC is better strategy for screening carriers and reduces further spread of thalassemia.