In this issue of the Revista Brasileira de Hematologia e Hemoterapia, Holanda et al. investigated the hypothesis that polymorphisms of the mannose-binding lectin 2 (MBL2) gene are associated with infections in patients with chronic lymphocytic leukemia (CLL). The authors did not find a correlation between genetic changes and frequency of infection in a cohort of 116 patients.

Patients with CLL have a highly variable clinical course: the majority will have a slowly progressive disease that will not require therapy for several years. However, a small but important minority will present with rapidly progressive disease. Continued efforts have aimed at identifying clinical and laboratory parameters that can predict the clinical evolution of CLL patients and their eventual need for treatment. Most clinicians still rely primarily on clinical staging systems (Rai and Binet) to determine the time for initial therapy. There are multiple laboratory parameters that have some degree of correlation with prognosis, including ZAP-70, the CD38 protein expression in CLL cells, and mutational status of the immunoglobulin heavy chain (IgVH) gene, but only the presence of cytogenetic abnormalities has been well validated and can be easily applied in clinical practice for assessment and prognosis.

CLL patients have immune abnormalities that increase the rate of infections as well as of autoimmune events. Most will experience an infectious event in the course of their disease, and approximately half will die from an infectious cause. The importance of infections cannot be understated, and identification of subjects who are at a particularly increased risk could guide preventive choices in the clinical management of CLL patients.

Mannose binding lectin (MBL) is a soluble protein that plays an important role in innate immunity. Polymorphisms in the promoter region and in exon 1 of the MBL2 gene affect MBL plasma concentrations. Holanda et al. investigated the correlation between polymorphisms of MBL2 and the rates of infection in 116 CLL patients. The clinical parameters that correlated with infection included CLL clinical stage and presence of splenomegaly. Most patients, regardless of whether they had infections, had MBL2 gene haplotypes associated with high or intermediate expression levels of MBL. There was no difference in the distribution of gene polymorphisms among patients with versus those without infectious complications.

The study was centered on a pertinent hypothesis, but the relatively small sample size prevented a definitive conclusion regarding the role of MBL2 gene polymorphisms and the risk of infection in CLL. The need for increasingly larger numbers of subjects in genetic studies is well-known in a variety of scenarios. As genetic testing identifies smaller subgroups carrying specific polymorphisms, statistically significance can only be achieved by studying very large cohorts of subjects.

Interpretation of infection data in CLL becomes more complicated due to the multifactorial nature of the immune dysfunction. Hypogammaglobulinemia is common and associated with progressive disease; various cell-mediated immunity defects have been identified and other parts of innate immunity, such as the complement system, are also...
abnormal.9 Only 7% of subjects in this study had haplotypes associated with low MBL expression. Therefore, it appears to be unlikely that MBL2 gene polymorphisms contribute to the risk of infection in most CLL patients.

The study by Holanda et al.1 highlights the difficulties in finding adequate predictive and prognostic factors in CLL. The heterogeneity of the patient population and the prolonged clinical course of the disease represent significant barriers to identify laboratory parameters that can be reliably utilized in the clinical practice.10 Large, longitudinal CLL patient databases and biorepositories will be fundamental for further advancement in the field of laboratory markers for this disease.

**Conflicts of interest**

The authors declare no conflicts of interest.

**REFERENCES**


