

**VINCENT RAJKUMAR:** I'm Vincent Rajkumar, professor of medicine in the division of hematology at Mayo Clinic. I'm talking about this study, looking at the prognostic value of serum free light chain in the general population. We studied about 16,000 patients who live in Olmsted County over the age of 50.

The assay consists of measuring the serum kappa and lambda free light chains. Normally, we make very small amounts of these light chains that can be detected. We had previously found that, in patients with clonal plasma cell disorders, elevations of the serum free light chains is predictive for progression to myeloma. And subsequently, my colleagues have shown that elevations of polyclonal levels of free light chains are predictive for death in patients with CLL, Hodgkin's disease, lymphoma, as well as myeloproliferative disorders.

In this particular study, we looked at whether elevations of serum free light chains are predictive for prognosis in the general population. We looked at nearly 16,000 patients. What we found, in other words, was that, in the next 10 years, the chances of being alive were more than 80% in patients with low levels of free light chain assay, but dropped to only about 30% to 35% in patients who had the highest deciles for free light chain.

We then looked at whether we can decipher what exactly was the mechanism for increased mortality. What we found was that mortality from almost all conditions was elevated in patients who had high levels of free light chains. So for example, there was a higher risk of deaths from cardiac causes, as well as neoplastic diseases, endocrine diseases, respiratory diseases, and so on.

The hypothesized mechanism by which we think high levels of free light chains are associated with higher risk of dying are that it's a marker for an immune overstimulation, as may occur in patients who have autoimmune disease or chronic infections or some other form of general hyperstimulation of the immune system, by which a polyclonal free light chain response is produced.

Another mechanism that we thought may be operational was renal failure. So we looked at whether the increased risk we found persisted after adjusting for renal failure. And we did find that the hazard ratio dropped to about twofold. But it still remained significant. Therefore, our finding was independent of renal function, as well as age and gender.

In the next few years, we hope to understand the mechanism by which high levels of free light chain are associated with a higher risk of mortality. And until then, we do not recommend that this be used as a screening test on the general population, but rather physicians should be aware of this so that in case this test is done for other reasons, one would be more well-equipped to interpret the results.

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