

The adult thymus reawakened: From healthy aging marker to immunotherapy biomarker

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Within the human immune system, the role of the thymus has long been insufficiently appreciated. The thymus is the central organ for T-lymphocyte development, maturation, and the generation of T-cell receptor (TCR) repertoire diversity. However, traditional views generally dictate that its physiological function is primarily concentrated in the embryonic and prepubertal stages. With advancing age, the thymus undergoes a progressive physiological process known as thymic involution. During this process, the highly immunocompetent cortical and medullary regions gradually atrophy and are replaced by extensive adipose and connective tissues. The adult thymus, especially in middle-aged and elderly populations, has therefore often been considered largely degenerated, with markedly diminished physiological significance in adult health maintenance and disease progression. More recent studies have linked extensive fatty thymic degeneration with obesity, lifestyle factors, and depletion of naïve CD8⁺ T cells,¹ while quantitative analyses of thymic involution and outcomes following adult thymectomy further support the persistent biological relevance of the thymus throughout adulthood.²⁻³ Only recently, propelled by the integration of deep learning technologies and large-cohort imaging data, has this long-standing immunological dogma finally reached a turning point.

Building on this emerging evidence, Bernatz and colleagues developed a

deep learning model using 5,674 chest CT scans to non-invasively quantify thymic health, an imaging-based proxy of thymic functionality derived from CT characteristics of the thymic region.⁴ They applied this algorithm across two large prospective cohorts, the Framingham Heart Study and the National Lung Screening Trial, to investigate the associations between thymic functionality and health. Among over 27,000 participants, higher thymic health emerged as a robust prognostic factor. It was significantly associated with lower all-cause mortality, cardiovascular disease and lung cancer incidence and mortality, as well as reduced mortality from various other endocrine, metabolic, and digestive diseases. Crucially, this AI-derived metric was also associated with the host's metabolic and lifestyle characteristics. Women and individuals with higher high-density lipoprotein levels exhibited better thymic health, whereas elevated triglycerides, high fasting glucose, hypertension, and a history of smoking were closely linked to worse thymic health. Furthermore, individuals with lower thymic scores showed a significant enrichment of pro-inflammatory proteins, such as IL-6 and CXCL family members, alongside chronically elevated C-reactive protein levels. This indicates a strong association between systemic inflammation and poor thymic health. Collectively, these observations support an association between metabolic and lifestyle perturbations, chronic systemic inflammation, and

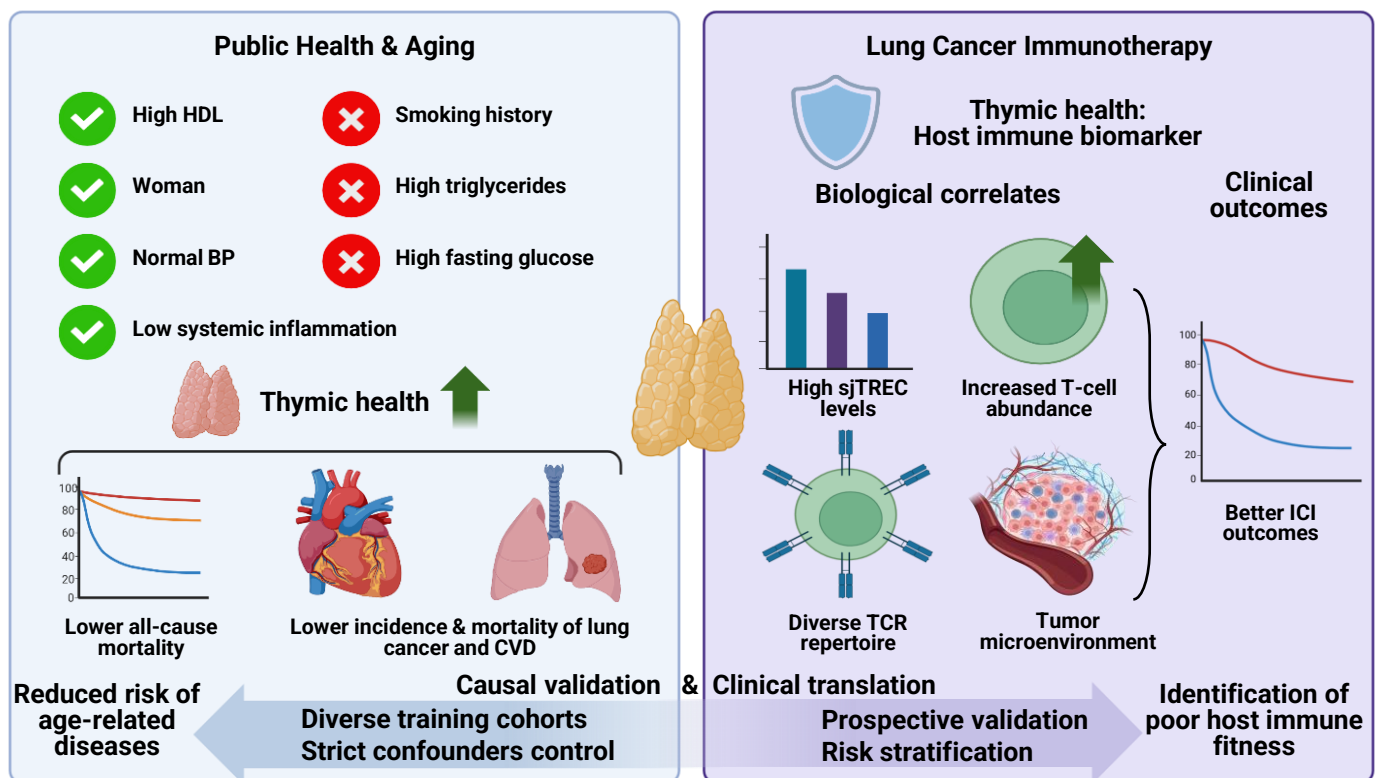


Figure 1. Thymic health as a candidate host immune biomarker of aging and immunotherapy outcomes Higher AI-derived thymic health scores are associated with healthier aging, lower disease risk, stronger host immunity and better outcomes among patients receiving cancer immunotherapy. Its causal role and clinical utility remain to be established. Image created in BioRender, with permission, <https://BioRender.com/3qlslxz>.

impaired thymic health, although the direction of causality remains unclear. However, a notable methodological limitation is the absence of formal mediation analysis or interaction tests. Without applying these statistical frameworks to quantify the direct and indirect effects, it remains unclear what proportion of the observed association with survival is causally mediated by thymic health versus the underlying lifestyle factors. Formal mediation analyses, longitudinal measurements, and mechanistic studies will be important to distinguish whether thymic health contributes directly to these outcomes or primarily serves as an integrative marker of healthier underlying biology. Overall, the current epidemiological evidence raises the possibility that modifiable metabolic and lifestyle factors may influence thymic health, although this hypothesis requires prospective validation before clinical intervention can be advocated (Figure 1).

The second study extends this scientific narrative from general disease risk to advanced cancer and, more broadly, from a predominantly tumor-centric framework toward host-centric immune assessment.⁵ Current immunotherapy biomarkers, including programmed cell death ligand 1 (PD-L1) and tumor mutational burden (TMB), are largely tumor-centric. They often fail to capture the host's systemic immune baseline. In contrast, thymic health offers a macroscopic window into the patient's holistic immune status. The researchers applied their AI imaging model to quantify thymic health non-invasively. They evaluated a cohort of patients with non-small cell lung cancer (NSCLC) receiving immune checkpoint inhibitors (ICIs). Lower thymic health was significantly associated with worse survival outcomes. This held true for both immunotherapy monotherapy and combination chem-immunotherapy. Subgroup analyses yielded consistent results. Thymic health stably stratified patient prognosis independently of classic tumor-intrinsic biomarkers like PD-L1 and TMB. Analyses of peripheral blood and the tumor microenvironment provided biological support. Patients with high thymic scores showed higher peripheral blood levels of sjTREC. They also demonstrated higher T-cell abundance and TCR diversity in circulation and within the tumor. These associations with sjTREC, T-cell abundance, and TCR diversity provide biological support linking the imaging-derived metric to residual thymic output and systemic immune competence, although they do not establish causality. Furthermore, the model revealed similar trends in a pan-cancer cohort. The lack of statistical significance in certain cancer types may partly reflect small sample sizes. Despite its clinical potential, this research remains an observational study. It currently lacks systematic experimental validation. A critical mechanistic uncertainty is the inability to rule out reverse causality. Impaired host thymic function might attenuate the antitumor immune response. Alternatively, a highly malignant tumor and prior toxic treatments might cause systemic consumption, accelerating thymic involution. Another important distinction is whether thymic health is specifically predictive of ICI benefit or primarily prognostic: because the principal cancer cohorts consisted of patients receiving ICIs, non-ICI comparator cohorts will be required to distinguish these roles. Nevertheless, this study provides a vital new perspective for precision oncology. It enables the early identification of patients with poorer host immune fitness and adverse prognosis. Clinicians could use this insight to identify high-risk patients for closer evaluation and prospective studies of alternative therapeutic strategies; however, thymic health alone should not currently be used to direct specific treatment choices (Figure 1).

Together, these studies move the field beyond the simple question of whether the adult thymus remains relevant and toward a more actionable one: how host immune fitness should be measured and incorporated into models of aging, disease risk, and treatment response. However, they leave the fundamental causal question unresolved: it is uncertain whether preserved thymic health directly contributes to better systemic and antitumor immunity, or whether it primarily serves as an integrative marker of healthier biology, lower inflammatory burden, and less aggressive disease. In other words, thymic health may represent either a biological determinant of immune competence or a surrogate marker integrating age, metabolic status,

inflammation, disease burden, and treatment exposure. This distinction matters clinically. If thymic integrity proves to be mechanistically important, treatment planning may need to account more explicitly for long-term effects on host immune competence, particularly for therapies with potential to damage thymic structure or function. If, instead, thymic decline mainly reflects tumour-driven or treatment-related systemic depletion, thymic health may still hold substantial value as a prognostic and stratification tool. In either case, these reports open a broader research agenda: defining when thymic health adds actionable information beyond existing biomarkers, clarifying how it interacts with treatment exposures, and determining whether similar principles extend to other lymphoid organs in systemic immune assessment. If impaired thymic health is found to directly degrade the tumor immune microenvironment, the thymus could emerge as an active therapeutic target, particularly in immunotherapy-dependent malignancies. This possibility could motivate the development of immune rejuvenation approaches, such as correcting metabolic disorders or reducing systemic inflammation, to delay thymic involution and overcome immunotherapy resistance. Conversely, if thymic decline is primarily driven by tumor-induced systemic consumption, the metric may primarily serve as a prognostic marker of systemic immune depletion rather than a directly targetable pathway. In this setting, its role would be to identify patients at increased risk rather than to justify any specific treatment intensification. The awakening of the adult thymus also encourages broader systemic immune profiling. It inspires broader questions regarding whether other primary or secondary lymphoid organs, such as the spleen, share similar protective functions, paving the way for the construction of a multi-dimensional, pan-organ immune evaluation system. As future prospective studies incorporate larger, ethnically diverse cohorts and detailed treatment histories, this AI-derived metric could become clinically relevant if they establish reproducible thresholds, generalizability, and incremental value over existing models. More broadly, these studies suggest that precision medicine may need to evaluate not only the tumor itself, but also the host immune system on which successful antitumor therapy depends.

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AUTHOR CONTRIBUTIONS

All authors contributed to and approved the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.