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Commentary on 'The Long-Term Mortality Predictors in Hypertrophic Cardiomyopathy Patients with Low Risk of Sudden Cardiac Death': A Call for Multidimensional Risk Stratification

'Ani Kalp Ölümü Riski Düşük Hipertrofik Kardiyomiyopati Hastalarında Uzun Dönemli Ölüm Tahmin Edicileri' Hakkında Yorum: Çok Boyutlu Risk Sınıflandırması Çağrısı

LETTER TO THE EDITOR
EDİTÖRE MEKTUP

To the Editor,

We read with great interest the recent publication by Kalenderoğlu et al.,[1] which provides crucial insights into the prognostic landscape of hypertrophic cardiomyopathy (HCM), specifically among patients classified as low risk for sudden cardiac death (SCD) based on HCM Risk-SCD scores. Importantly, we recognize that the primary endpoint of the study was all-cause mortality, not SCD itself; thus, any extrapolation to SCD risk modeling must be viewed as hypothesis-generating rather than definitive. Their study challenges the long-held clinical notion that low-risk HCM patients represent a uniformly benign population and highlights the need for refined risk stratification.

The authors identified advanced age, history of cerebrovascular accident, and elevated neutrophil count as independent predictors of long-term mortality, despite a baseline HCM Risk-SCD score < 4%. While neutrophil count reached statistical significance in multivariable analysis, the tertile-based comparisons showed no significant difference (P = 0.129). This discrepancy suggests that neutrophil count may exert its prognostic effect as a continuous variable, only becoming apparent after adjustment for confounders. Such nuances are critical for interpreting the role of inflammation in HCM.

We also emphasize that elevated neutrophil counts can arise from secondary causes such as acute infection, corticosteroid use, or hematologic disorders. Without systematically controlling for these factors, integration of neutrophil count into clinical risk scores may face challenges in translation to routine practice.

Moreover, the study's strength lies in its long-term, real-world follow-up. Nonetheless, several limitations must be acknowledged: the absence of cause-specific mortality data prevents distinguishing arrhythmic from non-arrhythmic deaths; lack of cardiac magnetic resonance imaging (MRI) precludes fibrosis quantification; omission of genetic testing leaves hereditary risk unexplored; and the absence of long-term rhythm monitoring limits insights into atrial fibrillation burden.[2] Recommendations for modifying risk models should therefore be framed in light of these constraints.

Particularly innovative is the identification of neutrophil count as an independent predictor of mortality—a finding that links systemic inflammation with both arrhythmic and non-arrhythmic pathways of disease progression. While the neutrophil-to-lymphocyte ratio has been previously correlated with adverse outcomes in HCM,[3] this is one of the first studies to isolate neutrophil count as a stand-alone marker in a low-risk cohort. We agree with the authors that this opens the door to exploring anti-inflammatory therapies (e.g., colchicine, interleukin-1 beta [IL-1β] blockade), but we stress that such proposals remain speculative and should be explicitly regarded as hypothesis-generating until tested in dedicated trials.

To build upon the valuable foundation laid by Kalenderoğlu et al.,[1] we suggest the following multidimensional future research pathways:

Schawanya Kaewpitoon Rattanapitoon[1]
Natnapa Heebkaew Padchasuwan[2]
Nav La[3]
Nathkapach Kaewpitoon Rattanapitoon[1]

[1]FMC Medical Center of Thailand, Nakhonratchasima, Thailand
[2]Khon Kaen University Faculty of Public Health, Khon Kaen, Thailand
[3]International University Faculty of Pediatric and Medicine, Phnom Penh, Cambodia

Corresponding author:
Schawanya Kaewpitoon Rattanapitoon
✉ schawanya.ratt@g.sut.ac.th

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1. Inflammatory Biomarker Integration: Investigating composite markers such as neutrophil extracellular traps (NETs), high-sensitivity C-reactive protein, and interleukin-6 may elucidate causal pathways linking inflammation to myocardial fibrosis and mortality in HCM.[4]
2. Machine Learning Models: Incorporating variables such as clinical features, frailty markers, echocardiographic data, atrial fibrillation burden, laboratory markers (including neutrophils), and cardiac magnetic resonance (CMR)-derived fibrosis into artificial intelligence (AI)-based prognostic tools—with attention to algorithm selection, training/validation schemes, and external validation—could yield individualized mortality predictions.
3. Holistic Risk Frameworks: Future scoring systems should include markers of frailty, systemic inflammation, and cerebrovascular risk, especially in elderly patients, who may fall outside the scope of traditional SCD-focused guidelines.
4. Longitudinal Imaging Correlates: The absence of cardiac MRI data in the present study limits interpretation of myocardial fibrosis burden. Future prospective cohorts should integrate late gadolinium enhancement quantification, T1 mapping, and strain imaging.
5. Therapeutic Implications: Future interventional studies should investigate whether modulation of inflammatory pathways can impact mortality or arrhythmic events in HCM, while recognizing that current evidence remains preliminary.

In conclusion, Kalenderoğlu et al. have provided important evidence that low-risk HCM patients are not a homogeneous group. Their study highlights predictors of all-cause mortality—advanced age, cerebrovascular history, and elevated neutrophils—that may not directly equate to SCD risk but nonetheless deserve consideration in future multidimensional risk models. Framing these findings as hypothesis-generating, we believe this work will catalyze more nuanced and personalized approaches to HCM management.

Conflict of Interest: The authors have no conflicts of interest to declare.

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