YKL-40 in Pediatric Asthma, MUC5B Promoter Polymorphism in Idiopathic Pulmonary Fibrosis, and Esmolol in Septic Shock

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Recommended Reading from the Washington University Pulmonary and Critical Care Fellowship Program; Tonya Russell, M.D., Program Director

Konradsen JR, et al. The Chitinase-Like Protein YKL-40: A Possible Biomarker of Inflammation and Airway Remodeling in Severe Pediatric Asthma. *J Allergy Clin Immunol* (1)

Reviewed by Hrishikesh S. Kulkarni

A significant hurdle in biomarker-based stratification of diseases is that biomarker levels are affected not only by the underlying disease, but also by the natural variation in the underlying genotype (2). The chitinase-like protein, YKL-40, regulates the formation of collagen fibrils and increases smooth muscle proliferation (1). It has also been linked with asthma and airway remodeling (2). Those having the wild-type genotype (CC) at the promoter single-nucleotide polymorphism (SNP) rs4950928 (−131C→G) in CHI3L1—the gene encoding for YKL-40—overexpress the protein and have elevated serum YKL-40 levels compared with CG or GG genotypes (2). Hence, Konradsen and colleagues (1) hypothesized that YKL-40 would accurately stratify subjects with asthma when corrected for the natural variability in its genotype (2).

In a case-control study, 34 children aged 6–18 years with severe, treatment-resistant asthma (TRA), 39 with controlled persistent asthma (CPA), and 27 healthy control subjects (HC) were characterized using blood cell counts and biomarkers, pulmonary function testing, exhaled nitric oxide, and asthma control questionnaires. DNA was analyzed for the SNP, rs4950928 (−131C→G). Bronchial wall thickening (BWT) was assessed semiquantitatively by high-resolution computerized tomography.

The authors found that neither FEV₁ % predicted nor serum YKL-40 could discriminate TRA from CPA. However, the clinical applicability of their findings lies in YKL-40 being significantly higher in TRA versus CPA despite no differences in FEV₁ %

predicted, when restricted to wild-type genotype (CC). In TRA, YKL-40 had a moderately significant correlation with both asthma control scores and BWT on high-resolution computerized tomography that strengthened when restricted to wild type (CC). Thus, the authors concluded that, when corrected for genotype, YKL-40, a biomarker with biological plausibility for airway remodeling, distinguishes TRA from CPA and robustly correlates with other markers for asthma control.

However, there are multiple limitations that prevent the immediate clinical implementation of YKL-40. These results cannot be applied to noncompliant children or those with difficult-to-treat asthma from identifiable causes, because they were excluded from this study. BWT was determined using a semiquantitative method, and was only measured in TRA. Given regional heterogeneity in airway remodeling, a more precise quantitative measure would have been more appropriate (3). In addition, there was a large overlap of YKL-40 levels between and within the different severity and genotype subgroups. Thus, further studies are needed to validate this promising biomarker. ■

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Peljo AL, et al. Association between the MUC5B Promoter Polymorphism and Survival in Patients with Idiopathic Pulmonary Fibrosis. JAMA (4)

Reviewed by Robert D. Guzy

Idiopathic pulmonary fibrosis (IPF) is a progressive disease, with a median survival of 3 years after diagnosis. IPF is one of the leading indications for lung transplantation. It is a heterogeneous disease with variable clinical decline, and current methods used to predict mortality are limited. Recently, a common polymorphism within the promoter region of the mucin gene, *MUC5B*, was associated with increased risk of familial and sporadic IPF (5). Although the T minor allele of *MUC5B* was associated with increased risk of developing IPF, the effect on mortality in patients with IPF was not known.

Peljo and colleagues (4) retrospectively analyzed two IPF cohorts—patients enrolled in the multicenter International Study of Survival Outcomes in Idiopathic Pulmonary Fibrosis with Interferon γ 1-b (INSPIRE) trial ($n = 438$) (6), and patients recruited from the Interstitial Lung Disease Clinic at the University of Chicago ($n = 148$). Genotyping of the *MUC5B* SNP, rs35705950, was performed in all patients from both cohorts. A primary analysis of the association between the *MUC5B* polymorphism and survival was performed initially on the INSPIRE cohort, and 2-year survival was higher in patients carrying one or more copies of the T minor allele of *MUC5B*. These results were validated in the Chicago cohort, and were still significant when accounting for the effects of sex, baseline FVC, baseline diffusing capacity of carbon monoxide, and matrix metalloproteinase-7 levels.

This study is the first report to describe a genetic polymorphism associated with improved survival in IPF. A major limitation is the relatively small cohorts, which limits precision of hazard ratios for death, and also limits interpretation of interactions with treatments or other biomarkers. Overall, this study provides a potential addition to our ability to predict mortality in patients with IPF, which affects clinical care and determination of timing for lung transplantation. This study raises important questions about the pathophysiology of IPF, particularly how a single polymorphism in the *MUC5B* gene confers both an increased risk of developing IPF and improved overall survival. We can speculate that alterations to mucin expression or function related to *MUC5B* polymorphism status may alter epithelial homeostasis and promote bronchiolization within areas of honeycombing, accounting for the increased risk of IPF. Conversely, the *MUC5B* polymorphism may somehow confer protection against IPF exacerbations, accounting for reduced mortality, although the frequency of exacerbations in patients with IPF carrying the T minor allele of *MUC5B* is not currently known. ■

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Morelli A, et al. Effect of Heart Rate Control with Esmolol on Hemodynamic and Clinical Outcomes in Patients with Septic Shock: A Randomized Clinical Trial. JAMA (7)

Reviewed by Colleen McEvoy

Septic shock is associated with high plasma catecholamine levels and tachycardia, which are independently associated with poor outcomes in critically ill patients (8–10). Beta blockade may help prevent sympathetic overstimulation, which may, in turn, enhance myocardial function and improve outcomes.

This single-center, open-label, randomized phase 2 study evaluated esmolol as a therapeutic intervention for heart rate control involving patients in septic shock with a heart rate greater than 95 beats/min, requiring high-dose norepinephrine (7). After 24 hours of hemodynamic optimization, 77 patients were randomly assigned to receive a continuous infusion of esmolol titrated to maintain a heart rate between 80 beats/min and 94 beats/min for their intensive care unit stay, and 77 patients to standard treatment. The study met the primary outcome goal of reduction in heart rate to below 95 beats/min, with a mean area under the curve of -28 beats/min in the esmolol group and -6 beats/min in the control group ($P < 0.001$). Secondary outcomes measured included hemodynamic and organ function measures, adverse events, and 28-day mortality. The stroke volume, systemic vascular resistance, and left ventricular stroke work indices were increased in the esmolol group. Mean arterial pressure was maintained even with a marked reduction in norepinephrine requirements in the esmolol group compared with the control group (-0.11 $\mu\text{g/kg/min}$ vs. -0.01 $\mu\text{g/kg/min}$; $P = 0.003$). In the esmolol group, kidney function was maintained and the arterial oxygen partial pressure/inspired oxygen fraction ratio was higher. Fluid requirements were significantly reduced in the esmolol group (mean area under the curve = $3,975$ ml/24 h vs. $4,425$ ml/24 h; $P < 0.001$). The 28-day mortality was significantly reduced in the esmolol group compared with the control group (49.4 vs. 80.5%; $P < 0.001$).

This study demonstrated that esmolol could effectively lower heart rate to the targeted range without further cardiac decompensation or worsening organ dysfunction. Beta blockade reduces the excessive sympathetic outflow and the toxic effects of catecholamines. The reduction in heart rate allows for longer ventricular filling during diastole, leading to increased stroke volume and improved myocardial oxygen consumption. A limitation of this study is the open-label, single-center, single-intensive care unit design with a small patient population, making it difficult to generalize these benefits. The study did not control for important determinants of outcome. For example, in an area with high endemic rates of multidrug-resistant *Klebsiella* and *Acinetobacter*, it is not known if patients received appropriate antibiotic therapy based on organism susceptibilities. The significant mortality benefit in the esmolol group is potentially important; however, these findings suggest the need for a large, multicenter trial. ■

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