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LETTER

Limitations in the Use of Cystatin C as a Predictor of Major Adverse Cardiovascular Events: Consideration of Non-Renal Factors [Letter]

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Dear editor

We reviewed Wasyanto et al's article titled "Cystatin C as a Predictor of Major Adverse Cardiovascular Event in Patients with Acute Myocardial Infarction Without Cardiogenic Shock and Renal Impairment After Coronary Intervention"[1] in the *International Journal of General Medicine* and applaud the authors on a successful publication. The study involved 40 patients with acute myocardial infarction (AMI) and examined the association between cystatin C levels and major adverse cardiovascular events (MACE) over a 6-month follow-up. Higher cystatin C levels at the time of AMI were associated with an increased risk of MACE, including death, reinfarction, heart failure, stroke, and dialysis. Cystatin C was considered a valuable predictor of MACE in patients with normal renal function, aiding in identifying high-risk patients for aggressive treatment. However, we believe this study has certain limitations that need to be addressed.

The study controlled for confounding factors like age, sex, smoking status, and BMI and excluded patients with chronic renal failure, malignancy, cardiogenic shock, pregnancy, and sepsis. However, uncontrolled factors such as inflammation, obesity, and hyperthyroidism may fog the association between cystatin C levels and MACE risk as they too are linked with high levels of serum cystatin C.

Apart from its primary role as a cysteine protease inhibitor, cystatin C has immune-related functions. It aids in processing pro-granzymes and other substances in immune cells, contributes to antigen presentation, promotes dendritic cell maturation, modulates integrin function, and plays a role in the development of the skin barrier, which acts as the body's first line of defense.[2] Therefore, inflammatory conditions can increase cystatin C production, leading to elevated levels in the blood even when renal function is normal. As inflammation is prevalent in multiple diseases, including cardiovascular conditions, this poses a challenge when using cystatin C as a predictive biomarker. Consequently, the association between cystatin C levels and adverse outcomes may be influenced more by the underlying inflammatory condition.

Similarly, obesity is linked to elevated cystatin C levels due to chronic low-grade inflammation in adipose tissue, which triggers increased production and release of cystatin C. Insulin resistance, prevalent in obesity, also contributes to higher cystatin C levels.[3] Furthermore, patients presenting with hyperthyroidism also display elevated base Cystatin C levels, attributed to the altered production rate of Cystatin C instead of a change in glomerular clearance,[4,5] a confounding factor that Wasyanto et al[1] did not take into account.

Non-renal factors, such as inflammation, obesity, and hyperthyroidism, can significantly impact cystatin C levels in patients with normal renal function. These factors can result in elevated cystatin C levels, so neglecting the influence of such factors on cystatin C levels can introduce a confounding factor in the study's findings. Hence, future research should aim to better understand and account for these non-renal factors.

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Disclosure

The authors report no conflicts of interest in this communication.

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