

# The Association of $\beta$ 2-Microglobulin and Fibroblast Growth Factor 23 with Major Adverse Cardiac Event in Acute Coronary Syndrome Patients with Chronic Kidney Disease

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## ABSTRAK

**Latar belakang:** penyakit ginjal kronik (PGK) diketahui meningkatkan keparahan dan mortalitas pada pasien sindrom koroner akut (SKA). Beta2-Mikroglobulin ( $\beta$ 2-M) sebagai penanda inflamasi dan fibroblast growth-factor 23 (FGF23) sebagai penanda CKD-bone mineral disorder (CKD-MBD) mungkin memiliki peran bermakna dalam proses patofisiologi pada pasien SKA dengan PGK. Penelitian ini bertujuan untuk mengetahui pengaruh  $\beta$ 2-M dan FGF23 terhadap major adverse cardiac event (MACE) pada pasien SKA dengan PGK. **Metode:** penelitian ini menggunakan desain potong-lintang dan kohort prospektif untuk kejadian MACE. Sampel penelitian merupakan pasien SKA dengan PGK yang dirawat di RSUPN Dr. Cipto Mangunkusumo pada periode Januari–Oktober 2018. Data dianalisis menggunakan regresi logistik dan Cox's proportional hazard regression. **Hasil:** sebanyak 117 subyek yang memenuhi kriteria pemilihan diikuti dalam penelitian. Kadar  $\beta$ 2-M, FGF23, dan derajat PGK secara bermakna berpengaruh terhadap MACE ( $p = 0.014$ ,  $p = 0.026$ ,  $p = 0.014$ ). Pada analisis multivariat, ditemukan  $\beta$ 2-M secara bermakna berpengaruh terhadap kejadian MACE (HR 2.16; IK 95% 1.15-4.05,  $p = 0.017$ ). **Kesimpulan:** dalam penelitian ini ditemukan bahwa  $\beta$ 2-M memiliki pengaruh bermakna terhadap MACE, sedangkan FGF23 tidak demikian. Temuan ini mendukung teori adanya peran inflamasi/peradangan dalam luaran kardiovaskular pada pasien SKA dengan PGK melalui efek akut pada kondisi kronik (acute on chronic effect).

**Kata kunci:** beta2-mikroglobulin, fibroblast growth factor 23, sindrom koroner akut, major adverse cardiac event.

## ABSTRACT

**Background:** chronic kidney disease (CKD) increases the severity and risk of mortality in acute coronary syndrome (ACS) patients. The role of  $\beta$ 2-M as a filtration and inflammation marker and FGF23 as a CKD-MBD

process marker might be significant in the pathophysiology in ACS with CKD patients. This study aims to determine the association of  $\beta$ 2-M and FGF23 with major adverse cardiac event (MACE) in ACS patients with CKD. **Methods:** we used cross sectional and retrospective cohort analysis for MACE. We collected ACS patients with CKD consecutively from January until October 2018 at Dr. Cipto Mangunkusumo General Hospital. Data were analyzed using logistic regression and Cox's Proportional Hazard Regression. **Results:** a total of 117 patients were selected according to the study criteria. In bivariate analysis,  $\beta$ 2-M, FGF23, and stage of CKD had significant association with MACE ( $p = 0.014$ ,  $p = 0.026$ ,  $p = 0.014$ , respectively). In multivariate analysis,  $\beta$ 2-M - but not FGF 23- was significantly associated with MACE (adjusted HR 2.16; CI95% 1.15–4.05;  $p = 0.017$ ). **Conclusion:**  $\beta$ 2-M was significantly associated with MACE, while FGF23 was not so. This finding supports the role of inflammation in cardiovascular outcomes in ACS with CKD patient through acute on chronic effect.

**Keywords:** beta2-microglobulin, fibroblast growth factor 23, acute coronary syndrome, major adverse cardiac event.

## INTRODUCTION

Cardiovascular disease is one of the main causes of death globally, and coronary artery disease (CAD) contributes to more than half of cardiovascular disease.<sup>1</sup> CAD manifests widely from asymptomatic to acute coronary syndrome (ACS). Based on previous studies, chronic kidney disease (CKD) increases the risk of severity and mortality in ACS patients. Bae EH et al.<sup>2</sup> reported 18% mortality in acute myocardium infarct patients with glomerulus filtration rate (GFR) <15 mL/min/1.73 m<sup>2</sup> compared to 1,2% in patients with GFR >90 mL/min/1.73 m<sup>2</sup>. CKD patients also have a high prevalence of congestive heart failure (CHF) which might be related to the progression of the remodeling process, left ventricle hypertrophy (LVH), and systolic and diastolic dysfunction.<sup>3</sup>

Several studies reported that chronic inflammatory process, through the increased chemotaxis and inflammatory mediator activities, resulted in endothelial injury and accelerated the atherosclerosis process.<sup>4</sup> Beta2-microglobulin ( $\beta$ 2-M) is a component of major histocompatibility complex (MHC) Class I, a polypeptide which potentially acts as a local and systemic inflammatory marker.<sup>5</sup> The increased level of  $\beta$ 2-M resulted in chronic inflammatory process and endothelial injury.<sup>6</sup> Elevated levels of  $\beta$ 2-M as high as 1.58 mg/L increase the risk of cardiovascular disease by 1.5 times and mortality by 1.8 times.<sup>7</sup> Liabeuf, et al.<sup>8</sup> reported  $\beta$ 2-M increases as the stage of CKD progresses, especially at stage 4.

Abnormal metabolism of minerals,

hyperparathyroidism, and Vitamin D deficiency in CKD patients, also known as chronic kidney disease – mineral bone disorders (CKD-MBD), was reported to be related to worse outcome in ACS patients with CKD. In CKD patients, FGF23 is thought to affect the metabolism of minerals (Vitamin D, parathyroid hormone, calcium, and phosphate), especially in patients with CKD-MBD. FGF23 level increases as CKD progresses.<sup>6</sup> Elevated levels of FGF23 might increase the risk of coronary severity through left ventricular hypertrophy (LVH), blood vessel calcification, and Klotho status deficiency.<sup>7</sup> Elevated FGF23 levels were also associated with major adverse cardiac event (MACE).<sup>9</sup> Common outcomes of ACS, widely known as MACE, consists of cardiovascular complications such as myocardial reinfarction, cerebrovascular disease and stroke, pericarditis, cardiogenic shock, heart failure, arrhythmia, sudden cardiac death, urgent coronary artery bypass graft (CABG), and repeated percutaneous coronary intervention (PCI) in one inpatient admission.<sup>10</sup>

The role of  $\beta$ 2-M as a filtration and inflammation marker and FGF23 as a CKD-MBD process marker might be significant in the pathophysiology in ACS with CKD patients, especially in relation to coronary severity and MACE. Patients with CKD have chronic inflammation and may develop CKD-MBD. These two processes, along with other causes, may cause atherosclerosis. Atherosclerosis eventually leads to coronary heart disease and causes remodeling and left ventricular hypertrophy. This sequence then leads to heart failure that can

result in major adverse cardiac events. In CKD patients, structures identical to bone tissue are occasionally found in atherosclerotic lesions. The active process of transformation of smooth muscle cells into osteoblast-like cells then results in vascular calcification.<sup>11</sup> Through the CKD-MBD pathway, remodeling and LVH can occur directly without going through the classic process of atherosclerosis. As a result, heart failure is more common, especially in advanced CKD.<sup>7</sup> The aim of this study is to determine the association of Beta2-Microglobulin ( $\beta$ 2-M) and Fibroblast Growth Factor 23 (FGF23) to major adverse cardiac event (MACE) in acute coronary syndrome (ACS) patients with chronic kidney disease (CKD).

## METHODS

### Study Subjects and Sample Size

Study subjects are ACS patients with CKD who were admitted to Dr. Cipto Mangunkusumo General Hospital Jakarta and underwent angiography between January and October 2018. We excluded patients with incomplete medical records and patients with severe comorbidities, such as acute stroke, hepatic cirrhosis, chronic inflammation disease, sepsis, autoimmune disease, and cancer. We also excluded patients lost to follow up.

### Study Design and Procedure

This was an observational study with cross sectional and retrospective cohort design for MACE. Data for this study were collected using consecutive sampling methods from January to October 2018. Data were acquired from the intensive cardiac care unit (ICCU) and internal medicine ward at Dr. Cipto Mangunkusumo General Hospital, Jakarta. The protocol of this study had been approved by the Ethics Committee Faculty of Medicine University of Indonesia with ethical approval no. 0128/UN2.F1/ETIK/2018 was issued on 12th February 2018.

Case definitions were based on clinical diagnosis. Acute coronary syndrome, which includes ST-Elevation myocardial infarction (STEMI), non ST-Elevation myocardial infarction (NSTEMI), and unstable angina pectoris (UAP), were diagnosed based on clinical symptoms,

electrocardiogram, echocardiography, and elevated cardiac enzymes. Chronic kidney disease was diagnosed based on clinical symptoms, elevated urea and creatinine serum, estimated GFR (eGFR) calculation, and evidence of kidney damage (presence of albuminuria and structural abnormalities in ultrasonography).  $\beta$ 2-M and FGF23 were obtained from blood samples and measured using the enzyme-linked immunosorbent assay (ELISA) method. Cut-off points for  $\beta$ 2-M and FGF23 were determined using receiver operating characteristic (ROC) analysis. MACE was followed up to 30 days after admission by reviewing medical records and communicating directly with patients.

### Data Analysis

Data normality testing was done using the Kolmogorov-Smirnov test. We initially did bivariate analysis using  $\chi^2$  test. P value < 0.05 was considered significant. Significant variables were included in multivariate analysis using Cox's Proportional Hazard Regression for MACE, adjusted for diabetes mellitus.

## RESULTS

From all patients diagnosed as ACS with CKD who underwent angiography in Dr. Cipto Mangunkusumo General Hospital from January to October 2018, a total of 117 patients, consisting of 91 males (77.8%) and 26 females (22.2%), were included in this study based on the criteria. The mean age in this study is 57.79 (SD 10.018) years old. MACE was observed in 39.3% of patients, with the most frequent events being congestive heart failure, mortality, and reinfarction. Total mortality in this study was 14.5%, however, based on CKD stages, mortality among patients with CKD stage 1–2, 3a–3b, and 4–5 was 7.35%, 17.85% and 33.3%, respectively. The most common risk factors from patient history were hypertension (65%), smoking history (62.4%), and diabetes mellitus (39.3%). Based on clinical diagnosis of ACS, 62.3% are STEMI, 18% are NSTEMI, and 19.7% are UAP. Based on eGFR, 81.2% patients had renal dysfunction and were predominantly in CKD stage 2. The mean of eGFR was 62.52 mL/minute/1.73 m<sup>2</sup>. (**Table 1**)

**Table 1.** Characteristic of study population.

Variables	N=117
Gender, male - n (%)	91 (77.8)
Age (years), mean (SD)	57.8 (10)
Risk factors, n (%)	
- Diabetes mellitus	46 (39.3)
- Dyslipidemia	35 (29.9)
- Hypertension	76 (65)
- Obesity	15 (12.8)
- Chronic kidney disease (anamnesis)	8 (6.8)
- Smoking	73 (62.4)
ACS Diagnosis, n (%)	
- STEMI	73 (62.3)
- NSTEMI	21 (18)
- UAP	23 (19.7)
CKD Stage, n (%)	
- 1	22 (18.8)
- 2	46 (39.4)
- 3a	16 (13.7)
- 3b	12 (10.2)
- 4	12 (10.2)
- 5	9 (7.7)
Kidney Function	
- eGFR, mL/min/1.73 m <sup>2</sup> , mean (SD)	62.5 (30.5)
- Urea, mg/dL median (interquartile range)	34 (25.2–51.6)
- Creatinine, mg/dL, median (interquartile range)	1.19 (0.98–1.76)
MACE, n (%)	46 (39.3)
- Mortality	17 (14.5)
- Stroke	6 (5.1)
- Cardiogenic shock	6 (5.1)
- Heart Failure	33 (28.3)
- Arrhythmia	9 (7.7)
- Myocardial reinfarction	17 (14.5)

MACE was followed up to 30 days after hospital admission and was recorded in 39.3% of patients. The most frequent events are congestive heart failure, mortality, and reinfarction. Seventeen patients died during the follow up period and the main causes of death were stroke, myocardial reinfarction, cardiogenic shock, and arrhythmia.

Cut-off point for  $\beta$ 2-M was determined at 2.66 mg/L (area under the curve/ AUC 0.665, sensitivity 63.83%, specificity 57.14%) using receiving operating curve (ROC) to MACE analysis. Cut-off point for FGF23 was

determined at 210.125 mg/L (AUC 0.564, sensitivity 70.21% and specificity 52.86%), also using ROC to MACE.  $\beta$ 2-M level was elevated in 56.4% patients with median 2.78 mg/L. FGF23 level was elevated in 51.3% patients with median 214.95 pg/mL.

Bivariate analysis results (**Table 2**) showed that  $\beta$ 2-M, FGF23, and stage of CKD were significant for MACE. In multivariate analysis for MACE using Cox's Proportional Hazard Regression (**Table 3**),  $\beta$ 2-M was found to be associated with MACE (HR 2.082 (1.113 – 3.895),  $p = 0.022$ ). Meanwhile, FGF23 was not associated with MACE (HR 1.749 (0.964 – 3.173),  $p = 0.066$ ).

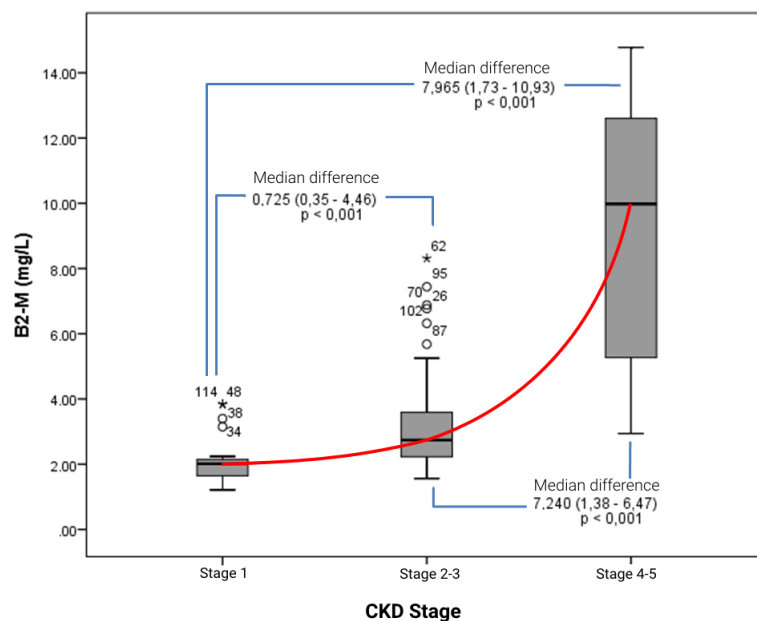
Further subgroup post hoc analysis showed significantly different  $\beta$ 2-M levels based on CKD stages. **Figure 1** shows the  $\beta$ 2-M elevation curve and median differences based on CKD

**Table 2.** Bivariate analysis for MACE.

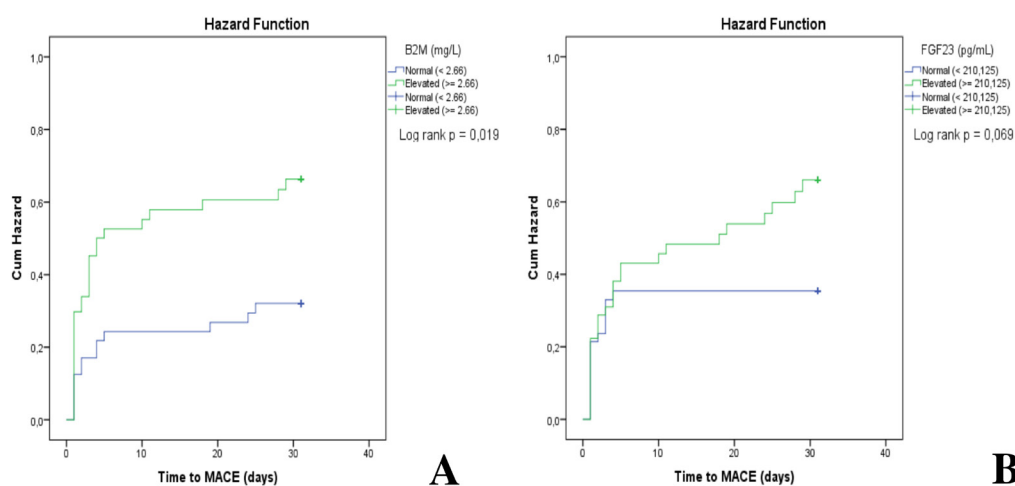
Variables	MACE	
	OR (CI 95%)	P value
Main independent variables		
- $\beta$ 2-M	2.643 (1.209–5.775)	0.014
- FGF23	2.353 (1.1–5.033)	0.026
Clinical variables		
- GRACE score		0.057
- ACS type	1.920 (0.895–4.120)	0.092
- CKD stage		0.014
Echocardiography variables		
- LV systolic function	0.504 (0.234–1.086)	0.078
- LVH	0.673 (0.313–1.444)	0.308
- LVH type		0.509
- LV Dilatation	2.211 (0.887–5.514)	0.085
- LV diastolic function		0.095
- LA dilatation	3.045 (1.077–8.607)	0.096
- RV systolic function	0.519 (0.229–1.176)	0.095

**Table 3.** Multivariate analysis, Cox's proportional Hazard regression of  $\beta$ 2-M and FGF23 to MACE.

Variables	HR (CI 95%)	P value	HR Changes
$\beta$ 2-M			
- Crude HR	2.08 (1.11 – 3.89)	0.022	
- Adjusted HR			
+ Diabetes mellitus	2.16 (1.15 – 4.05)	0.017	3.56%
FGF23			
- Crude HR	1.75 (0.96 – 3.17)	0.066	



**Figure 1.** Median difference of Beta-2 Microglobulin level based on CKD stages.



**Figure 2.** Hazard function showing hazard ratio difference between high and normal level  $\beta$ 2-M (A) and FGF23 (B) in ACS patients with CKD.

stages. It should be noted that there was a spike in elevation after CKD stage 4. There was no significant difference in FGF23 levels in all CKD stages. Independent t test was used to further evaluate the difference between  $\beta$ 2-M and FGF23 levels based on MACE. There was a significant difference in  $\beta$ 2-M level based on MACE occurrence (mean difference 1.597 mg/L,  $p = 0.006$ ), whereas there was no significant difference in FGF23 level.

Hazard function analysis for MACE in 30 days using a Kaplan-Meier Curve (**Figure 2**)

showed a hazard difference between normal and elevated  $\beta$ 2-M groups (logrank  $p = 0.019$ ). However, in normal and elevated FGF23 groups, there were intersecting events during the first 5 days between the two groups, and after 5 days there were no events in the normal FGF23 group (log rank  $p = 0.069$ ).

### DISCUSSION

To the best of our knowledge, this is the first study investigating the role of  $\beta$ 2-M and FGF23 in ACS patients with CKD. The patients



in this study were in mild to severe conditions. This might be due to the status of Dr. Cipto Mangunkusumo General Hospital as a national tertiary hospital which generally accepts referral patients in more severe condition from secondary hospitals. Total mortality in this study was 14.5%, with increasing percentage in higher CKD stage. This finding is in accordance with another study that reported the mortality in ACS patients with GFR <15 mL/min/1.73m<sup>2</sup> (18.3%) were higher than patients with normal GFR (1.2%).<sup>6</sup>

As previously mentioned,  $\beta$ 2-M, a cell membrane stabilizer, was a potential inflammatory mediator in local and systemic condition.<sup>5</sup>  $\beta$ 2-M, cystatin C and glucose level contribute to the process of atherosclerosis formation.<sup>6</sup> Glucose level affects the formation of advance glycation end products (AGEs).<sup>12</sup> AGEs could modify  $\beta$ 2-M and affect the mechanism of endothelial injury. The modified  $\beta$ 2-M causes an increase in chemotaxis activity, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-1 $\beta$  (IL-1 $\beta$ ) and interleukin-6 (IL-6), which leads to chronic inflammation process and endothelial injury. Further mechanisms include macrophage and lymphocyte recruitment, which accelerate the atherosclerosis plaque formation and blood vessel rigidity. The findings in this study might be caused by the characteristics of the patients, who predominantly experienced STEMI. STEMI is often related to the mechanism of thrombus disruption and thromboembolism, rather than endothelial rigidity. The thrombus disruption and thromboembolism mechanism results in predominantly single vessel disease. STEMI is usually caused by obstruction in main vessels and the risk of plaque disruption depends on the composition, the activity of the connective tissue in the plaque, and plaque size. Over half of infarct conditions are related to thrombus, which causes stenosis, vasoconstriction, inflammation, thrombosis, and embolization. The extent of myocardial necrosis is also related to the location and duration of obstruction, myocardial area and the presence of collateral vessels.<sup>13</sup>

Meanwhile, FGF23 was mainly related to remodeling processes which affect the development of Left Ventricle Hypertrophy and lead to congestive heart failure. Several studies

reported that FGF23 could induce cardiomyocyte hypertrophy through the PLC (phospholipase C)- $\gamma$ -calcineurin-NFAT (nuclear factor of activated T cell) signaling pathway. FGF23 is thought to activate Klotho-independent FGF Receptor-4 (FGFR-4), a specific receptor in cardiomyocyte, and subsequently induce a remodeling process, resulting in LVH.<sup>3,9,14</sup> According to Deo R. et al., LVH might cause dysfunction in diastolic function and atrial fibrillation.<sup>15</sup>

Cut-off points for  $\beta$ 2-M were described in several studies. In this study, the best cut-off point available was determined to be 2.66 mg/L with sensitivity 70.21% and specificity 52.86%. To get a more reliable cut-off point, a larger sample size would be required. Several studies have attempted to determine the cut-off point for FGF23, but proper and reliable cut-off point is yet to be determined. This might be caused by the wide range of possible FGF23 levels. For this study, the cut-off point for FGF23 was determined to be 210.125 mg/L with sensitivity 63.83% and specificity 57.14%.

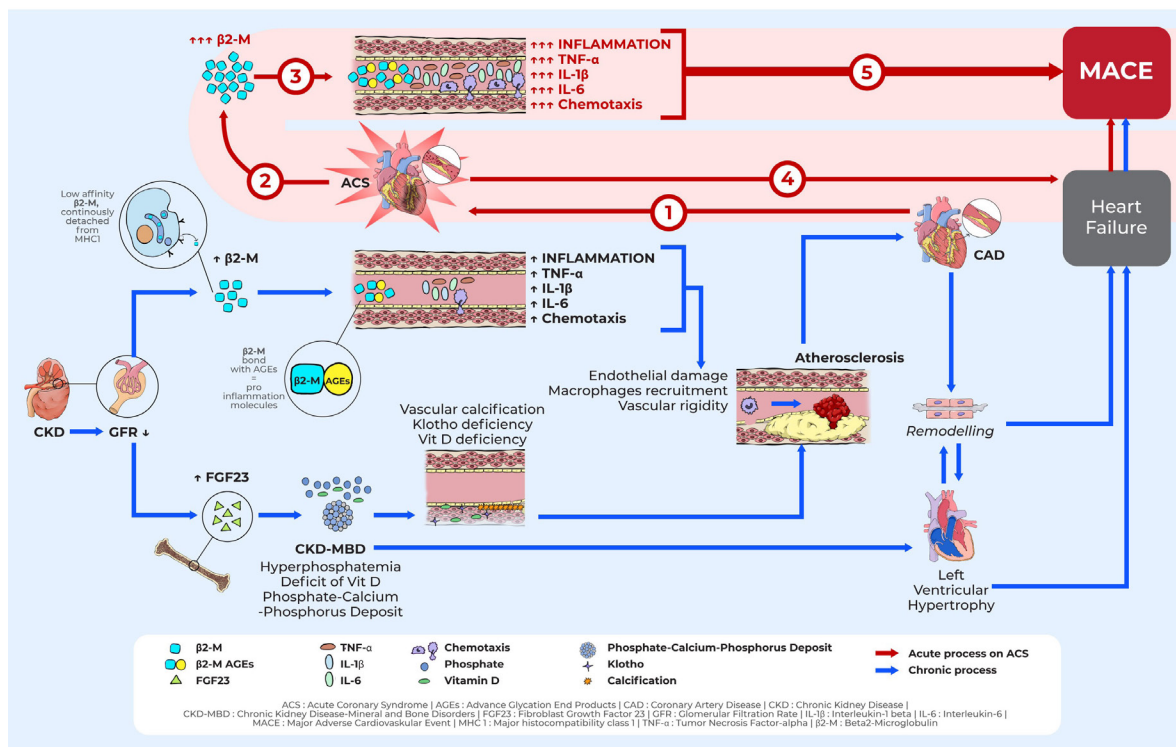
Our study found that  $\beta$ 2-M was associated with MACE. Hazard function with Kaplan-Meier curve showed significant difference of MACE occurrence in normal and elevated  $\beta$ 2-M groups and posthoc subgroup analysis also found a significant difference in  $\beta$ 2-M level based on CKD stages. A study by Jin et al. found that monocytes incubated with  $\beta$ 2-M exhibit a decrease in antigen presenting capacity and decreased T cell type I response. However, the growth and activity of those monocytes were stimulated by the increase in IL-6 and IL-10. Thus,  $\beta$ 2-M might affect the humoral immune system and promote inflammatory response.<sup>16</sup> A study by Liabeuf et al.<sup>8</sup> also found a significant difference in  $\beta$ 2-M level based on CKD stages in CKD-only patients. However, when compared, the results in this study form a steeper curve, with a notable spike of  $\beta$ 2-M after CKD stage 4. These findings support the role of  $\beta$ 2-M to promote greater inflammatory response in an acute state in ACS patients, especially if it occurs in an existing chronic inflammation state such as in CKD patients.

Meanwhile, FGF23 was not found to be associated with MACE. Hazard function curve

and subgroup analysis yield similar results. This might be due to the study design that observed patients in acute state when ACS occurred, meaning any FGF23 elevation before ACS occurred was not observed. Furthermore, observation and follow up duration in other studies were longer. FGF23 might only reflect chronic conditions, which would increase over time as CKD progresses,<sup>3</sup> while patients observed in this study were in an acute state. This difference could affect the measurements and yield different results from previous studies. Previous studies found a significant effect of FGF23 on cardiovascular risks in patients without acute condition over a longer observation duration.<sup>3,12,17</sup> Gutierrez et al.<sup>23</sup> and another cohort study with 2 year observation also reported that increased FGF23 level is associated with mortality.

This study met the minimum sample requirement according to initial calculation. However, some variables showed abnormal distribution, especially FGF23. The wide range of FGF23 level and lack of further dilution might affect the results of this study.

Based on the results of our study, we formulated a theory of mechanism of acute inflammation in ACS patients with CKD. **Figure 3** illustrates how CKD patients undergo chronic inflammation and CKD-MBD, indicated by the increased of  $\beta$ 2-M and FGF23 level. These processes, along with other classical mechanisms such as diabetes, lead to atherosclerosis, which results in coronary heart disease. Subsequently, coronary heart disease might trigger cardiac remodeling and left ventricle hypertrophy, which in the end will increase the risk of MACE.



**Figure 3.** Mechanism of inflammation in acute coronary syndrome patient with chronic kidney disease on MACE. (1) In the event of ACS, acute rupture of atheromal plaque causes ACS, (2) which raises  $\beta$ 2-M level in systemic circulation, which increases in accordance to the severity of CKD. (3) High level of  $\beta$ 2-M triggers systemic acute inflammatory process (4) Through rising of TNF- $\alpha$ , IL-1B, IL-6 and chemotaxis. Acute condition of ACS may trigger acute heart failure which can cause MACE. (5) This acute inflammation causes raised MACE prevalence in ACS patient with CKD. Abbreviations: ACS, acute coronary syndrome; CKD, chronic kidney disease; IL, interleukin; MACE, major adverse cardiac event; TNF, tumor necrosis factor.

## CONCLUSION

In this study we found that  $\beta$ 2-M was significantly associated with MACE 30 days after hospital admission, while FGF23 was not. These findings support the role of inflammation in cardiovascular outcomes in ACS with CKD patients through acute on chronic effect.  $\beta$ 2-M and FGF23 might be associated with myocardial remodeling processes, which subsequently cause left ventricle hypertrophy and congestive heart failure.

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