The role of suppression of tumorigenicity-2 on the quality of life of patients with heart failure

Starry H Rampengan¹, Janry A Pangemanan², Johan Gunadi³, Nancy Lampus¹

ABSTRACT

Heart failure is a clinical syndrome caused by structural and cardiac functional disorders and is the final phase of all cardiac diseases. Numerous studies have been conducted to assess cardiac biomarkers such as suppression of tumorigenicity-2 (ST2), galectin-3 (Gal-3), and high-sensitivity cardiac troponin (hs-cTn) and their ability in predicting the prognosis and risk stratification of heart failure. Suppression of tumorigenicity-2 is one of the biomarkers that are able to portray cardiac fibrosis and remodeling, as well as to predict cardiovascular events, rehospitalization, and cardiac death. Moreover, ST2 can also be used to evaluate the prognosis of heart failure and therapeutic response. The most convenient functional capacity assessment is the six-minute walking test (6MWT).

Besides 6MWT, two-minutes walking test (2MWT) is a most commonly performed alternative, particularly on elderly patients, patients with motoric disorders, and patients who had walking disturbance for a relatively long time. Cardiac failure compromises the functional capacity and ultimately the quality of life (QoL) of the patients. There are many questionnaires formulated to assess patients’ QoL, ranging from QoL in general to QoL specifically transcribed for patients with heart failure. To date, Minnesota Living with Heart Failure Questionnaire (MLHFQ) is the most frequently used questionnaire, as it comprises physical, emotional, and social aspects that are correlated with the functional capacity of the patients.

INTRODUCTION

Heart failure is the final stage of all cardiac diseases, namely when the damage to cardiac muscles had caused detrimental effects towards activity tolerance and quality of life (QoL).¹ Annually, more than 650,000 new cases of heart failure are diagnosed in the United States of America.²³ The number of patients with heart failure rises along with the increase of the age, approximately 20 patients per 1000 person in the 65-69 years old population, to more than 80 patients per 1000 person in more than 85 years old population.⁴ According to Indonesia’s National Report on Basic Health Research (RISKESDAS) 2013, the prevalence of cardiac diseases in the 65-74 age group is 0.5%, which grows to 1.1% in ≥75 age group.⁵ Coronary heart disease and hypertension were the main risk factors with the prevalence of 1.5% and 25.8%, respectively.⁶

Nowadays, there are various biomarkers that could evaluate the cardiac muscle injury and the prognosis of heart failure. Suppression of tumorigenicity-2 (ST2) is one of the biomarkers that are capable of depicting fibrosis and remodeling of cardiac muscle.⁷ ST2 predicts heart failure occurrences, rehospitalization, cardiovascular adverse events, and cardiac deaths. Monitoring of ST2 levels is beneficial in judging the therapeutic response and representing the clinical improvement of the disease.⁸

The diminution in cardiac output of patients with heart failure leads to the diminishing of patients’ functional capacity. The six-minute walk test (6MWT) is a modality to measure functional capacity in patients with heart failure that is considerably easy, affordable, and safe to perform. The 6MWT is a submaximal exercise test, which provides an estimation of daily activity.⁹¹⁰ Left ventricular dysfunction affects the physical ability to carry and utilize oxygen, which indirectly impacts functional capacity in 6MWT.¹⁰ The two-minute walk test (2MWT) can be used as an alternative to 6MWT in older patients, patients with motoric disorders, and patients who had walking disturbances for a relatively long period.¹¹

The functional capacity decline in patients with heart failure will also deteriorate the QoL. Furthermore, the diminishing of QoL in patients with heart failure increases the morbidity and the rehospitalization rate.¹²
HEART FAILURE

Definition and Classification

The American Heart Society (AHA) described heart failure as a complex clinical syndrome resulting from functional and structural damage of the heart, as the ventricular filling and pumping function is impaired. In addition, the European Society of Cardiology (ESC) defined heart failure as a clinical syndrome that is characterized by typical symptoms of shortness of breath, lower extremity swelling, and fatigue. Clinical signs such as increased jugular vein pressure, rhonchi, peripheral edema can also be found on physical examination, as a consequence of the decrease in cardiac output and the increase in either resting or loaded cardiac pressure.

According to Indonesian Heart Association, (hereafter abbreviated as IHA, locally known as PERKI) described heart failure as an array of symptoms such as breathing difficulty either when lying down or doing exercise, fatigue and weakness, and lower extremity swelling. The symptoms are accompanied by typical clinical signs of heart failure, including tachycardia, tachypnea, rhonchi on lung auscultation, pleural effusion, jugular vein pressure increase, peripheral edema, hepatomegaly; and objective findings of structural and functional impairment of the heart, third heard sound, heart murmurs, abnormality in echocardiography examinations, and raised natriuretic peptide levels.

Heart failure is categorized into three groups in relation to the ejection fraction, which are heart failure with preserved ejection fraction (HFpEF), heart failure with mid-range ejection fraction (HFmrEF), and heart failure with reduced ejection fraction (HFrEF), as described in Table 1.

Furthermore, functional capacity classification in heart failure refers to the New York Heart Association (NYHA) Functional Classification, which are based on the symptoms (fatigue, palpitation, and shortness of breath) and physical activity limitation in regard to the degree of the activity. There are four classes of functional capacity; NYHA Class 1: No limitation of physical activity, daily activity does not rise the symptoms; NYHA Class 2: Slight limitation of physical activity, patient is comfortable at rest, however, symptoms arise on daily activity; NYHA Class 3: Marked limitation of physical activity, patient is comfortable at rest but activities lighter than daily activity arise symptoms; NYHA Class 4: Unable to perform any physical activity without discomfort, and discomfort increases as any physical activity is performed.

Etiology and Pathophysiology

Causes of heart failure can be categorized into (1) Impaired ventricular contractility, (2) Increased afterload, (3) Relaxation and ventricular filling disorders. Coronary heart disease is the cause of about two-thirds of systolic heart failure cases, in addition to hypertension and diabetes mellitus. Other causes include viral infections, alcohol, chemotherapy and idiopathic cardiomyopathy.

The decrease in cardiac output in heart failure will activate the neurohormonal system, the sympathetic nervous system, and the Renin-Angiotensin-Aldosterone (RAA) system. The activated neurohormonal system results in water and salt retention, as well as vasoconstriction and remodeling processes that adversely affect the cardiovascular system. Increased sympathetic nerve activation increases the amount of norepinephrine in the circulation, which is associated with a poor prognosis. The β-adrenergic receptor will also be activated, thereby increasing the heart rate and contractility of the myocardium. Moreover, α-adrenergic receptors are also activated and thus increase the inotropic effect and vasoconstriction in peripheral arteries. Those effects increase the afterload and heart's oxygen demand, which may trigger ischemic condition of the heart.

The activation of RAA system will produce angiotensin II, which will bind to angiotensin II type 1 receptors (AT1) and angiotensin II type 2 receptors (AT2). Both of these receptor subtypes are present in the myocardium with a greater distribution of AT2 than AT1. AT1 triggers vasoconstriction, induces cell growth, aldosterone secretion, and catecholamine release. On the

Table 1. ESC Classification of Heart Failure based on Ejection Fraction

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<th>Criteria</th>
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<td>1</td>
<td>Symptoms ± Signs</td>
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<td>Symptoms ± Signs</td>
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<tr>
<td>2</td>
<td>LVEF &lt; 40%</td>
<td>LVEF 40-49%</td>
<td>LVEF ≥ 50%</td>
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<tr>
<td>3</td>
<td>1. Increased natriuretic peptides levels</td>
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other hand, AT2 oppose those effects, and triggers vasodilatation, inhibits cell growth, decreases the natriuresis and the release of bradykinin.\textsuperscript{16-18}

The inflammatory process becomes one of the factors that exacerbate the progression of the heart failure syndrome. Various inflammatory mediator cytokines that play an important role are tumor necrosis factor-alpha (TNF-\(\alpha\)), interleukin 1 (IL-1) and interleukin 6 (IL-6). One of the possible mechanisms occurred is the overproduction of cytokines that is triggered by catecholamines.\textsuperscript{18}

**SUPPRESSION OF TUMORIGENICITY (ST2)**

**Biological Features of ST2**

ST2 is a peptide of the interleukin-1 (IL-1) receptor group, secreted when cardiomyocytes and cardiac fibroblasts are exposed to mechanical strains. ST2 have three primary isoforms of transmembrane isoform (ST2L), secreted soluble (sST2), and a variant of IL-1 expressed in the gastrointestinal tract (stomach, small intestine, and colon).\textsuperscript{19} ST2 triggers myocyte hypertrophy and cardiac fibrosis involving ST2L, sST2, and IL-33 ligand.

**Cardiac Remodeling and the Role of ST2**

Remodeling is an unfavorable process because it is closely related to the deleterious cardiac functional prognosis and clinical manifestations. Those detrimental effects are due to the injury of cardiomyocytes that interfere its ability to contract normally. Damages occurring at the cellular level include decrease in the alpha myocyte and myofilaments chains, alteration in the cardiomyocyte cytoskeleton structure, changes in energy metabolism, and desensitization of \(\beta\)-adrenergic receptors.\textsuperscript{18}

Several experimental studies have demonstrated a linked pathophysiological mechanism between cardiac remodeling and ST2/IL-33. Studies by Sanada et al. showed the role of IL-33 and ST2 in heart remodeling in mice exposed to excessive physical force.\textsuperscript{20} Miller et al. also reported a decrease in the formation of the atherosclerotic plaque of aorta in mice fed a high-fat diet with IL-33 therapy. On the other hand, the process rapidly increases with the administration of ST2.\textsuperscript{21} In the study of the cardioprotective effects of IL-33/ST2L on myocardial ischemia, in vitro trial found that IL-33 reduced the incidence cardiac myocytes apoptosis and the effect was reduced by giving sST2. In addition, in vivo studies of IL-33 administration showed faster recovery in the mice's hearts after myocardial infarction, whereas the therapy was slowed down with ST2 administration.\textsuperscript{22}

Suppression of Tumorgenicity-2 is a receptor of IL-33. IL-33 that binds to ST2L has cardioprotective effects, reduces fibrosis and myocardial hypertrophy through the NF-kB pathway. The activity of IL-33/ST2L complex involves the IL-1 RaCp co-receptor bond, including the interleukin Toll receptor that involved in the intracellular signaling. The adaptor proteins of MyD88 are further involved and NF-kB is activated through IRAK-1 and IRAK-4 as well as TRAF6, which trigger the release of inflammatory mediators. The cardioprotective effect only occurs when IL-33 binds to ST2L instead of binding to sST2. Moreover, sST2 acts as antagonist and prevents IL-33 binding to ST2L, thus inhibiting its cardioprotective effect.\textsuperscript{23,24} The role of sST2 in heart failure is similar to that of HbA1C in blood sugar control. Adequate blood sugar control will lower HbA1c levels into the range of levels that give better prognostics. Likewise, robust control of heart failure will decrease the sST2.\textsuperscript{24}

**Clinical Application of ST2 Level Measurement**

Based on the 2017 American Heart Association/American College of Cardiology Foundation (ACCF/AHA) guidelines in 2017, cardiac marker examinations that predict cardiac damage or...
ranges were found in healthy populations in the United States using the similar analysis, 8.6-49.3 in males and 7.2-33.5 in women, and the levels are not age-related. \textsuperscript{27} Soluble-ST2 is not correlated with sex, age, body mass index, and other underlying causes of heart failure, atrial fibrillation and anemia. Unlike other cardiac markers affected by renal function, sST2 is hardly affected by renal function. \textsuperscript{28}

In patients with heart disease, the use of ST2 as an additional prognostic biomarker has been widely reported. In the PRIDE study, sST2 levels were found to be higher in the population with acute HF compared to them in the healthy population. Similar result was also described in the population with arterial pulmonary hypertension, with a significant correlation between the sST2 levels and the severity of heart failure symptoms (based on NYHA categories), which is essential in determining its prognosis. \textsuperscript{28}

Soluble-ST2 and Rehospitalization Rate

Elevation of sST2 concentrations in chronic heart failure are closely related to severity, increased risk of death, transplantation rate, sudden deaths and cardiovascular events such as rehospitalization. \textsuperscript{29, 30}

In the study by Ky et al., in patients with chronic stable heart failure, an increase in sST2 was found and was associated with an increased risk of death and transplantation in the monitoring of approximately 2.8 years. \textsuperscript{31} Similar results were also described by Vorovick et al., which found that during the 4-year monitoring, the increase of sST2 levels could be an independent predictor of rehospitalization. \textsuperscript{32}

Large multicenter trials investigating sST2 such as CORONA, HF-Action, Val-HeFT have also reported that the increase in sST2 is associated with future cardiovascular events. \textsuperscript{33-35}

The target of sST2 in patients with heart failure in ambulatory care was 35 ng/mL. \textsuperscript{10}

Heart failure treatment outcome can be monitored by measurement of sST2. Changes in the value of sST2 during heart failure therapy can predict mortality in 90 days. \textsuperscript{36} Bayes et al. measured the baseline and 2-weeks post-treatment values of sST2 and NT-proBNP in decompensated acute heart failure patients. The sST2 ratio was found to be associated with rehospitalization, heart transplantation, and death within one year of follow up. Inversely, decreased sST2 after two weeks was associated with clinical improvement and a significant drop in sST2 levels were found in patients without cardiovascular events rates within two weeks of ambulatory care. \textsuperscript{37} The PROTECT study measured sST2 levels at baseline and after three, six and nine months in stable chronic heart failure patients, showed that sST2 could be used in risk stratiﬁcation (Figure 6). Soluble ST2 is a marker in predicting rehospitalization and death in patients with heart failure. \textsuperscript{25}

Dieplinger et al. reported the value interval of ST2 in healthy Austrian populations of 4-31 ng/mL in men and 2-21 ng/mL in women. \textsuperscript{26} Higher value

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**Figure 1.** The role of ST2 in cardiac remodeling (Cited from: Maisel AS, Di Somma S. Do we need another heart failure biomarker: focus on soluble suppression of tumorigenicity 2 (sST2). European heart journal. 2016:ehw462) \textsuperscript{24}

**Figure 1.** Indications for the use of cardiac biomarkers (Quoted from: Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Colvin MM, et al., 2017 ACC/AHA/HFSA Focused update for the management of heart failure: a report of the American College of Cardiology / American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America Circulation 2017) \textsuperscript{25}
provide prognostic information and predict future cardiovascular events. 

QUALITY OF LIFE OF HEART FAILURE PATIENTS

To date, the definition of quality of life (QoL) in chronic heart failure and acute heart failure has not been clearly described. The QoL of the patients can be assessed from several parameters such as functional capacity, physical activity ability, psychological status, and frequency of hospitalization or rehospitalization. Patients with progressive heart failure typically have decreased QoL and increased rehospitalization rate. Therefore, the treatment of heart failure is mainly aimed to improve the QoL of the patients. Studies were conducted to assess the efficacy of therapy in improving patients’ QoL as well as the correlation between functional capacity and patients’ QoL. The QoL decreases as functional capacity decreases and morbidity increases.

Functional Capacity and Physical Activity Capability

Functional capacity and physical activity capability can be assessed by cardiac exercise tests, such as treadmill test, ergocycle or static bicycle, and walk tests. Walk test is an easy, inexpensive modality that could describe functional capacity in patients with heart failure. The six-minute walk test is a submaximal cardiac exercise test that illustrates the daily activity of the patient.

Walk Tests

The six-minute walk test (6MWT) is the most commonly used protocol compared to other walk tests. This test was first introduced in 1963 by Balke and is often used in various clinical circumstances since the mid-1980s. This 6MWT was initially used in patients with pulmonary diseases, but now has been implemented in patients with cardiovascular diseases, neurological disorders, fibromyalgia and muscular atrophy, and post-surgery recovery patients. Physical capacity and physical tolerance are important factors in assessing the clinical and prognostic conditions of cardiovascular patients.

Six-Minute Walk Test

The six-minute walk test is a submaximal cardiac exercise test; hence it can describe patients’ ability to perform their daily activity. In the study by Gibbons et al. in young participants with mean age of 45.1 years, the average distance of 6MWT was 689 meters in men and 615 meters in women. Another study on participants with the mean age of 65 years old was conducted by Troosters et al., obtained an average distance of 613 meters among all participants, and an average distance of 656 meters in men and 554 meters in women. Stefen et al. also reported the results of 6MWT in the elderly participants with an average age of 74.1 years old, and obtained results of 505 meters in men and 467 meters in women. The resulting distance of 6MWT can be used to derive VO2 and patients’ metabolic equivalents (MET) and ultimately their functional capacity.

In patients with heart failure, the results of their 6MWT can be used as a prognostic factor. Heart failure patients with a low 6MWT range were associated with increased mortality and rehospitalization. Several studies have been conducted to assess the prognostic function of 6MWT as well as its function in predicting mortality and rehospitalization in patients with heart failure. The Study of Left Ventricular Dysfunction (SOLVD) by Bittner et al. was the first study reporting mortality rates of 10.23% in patients with 6MWT distance less than 350 meters and 2.99% in patients with 6MWT distance over 450 meters. In 2010, Pollentier et al. carried out a review of 14 researches on 6MWT to evaluate its reliability and validity in predicting functional capacity of chronic heart failure patients, with the result that 6MWT has a good reliability, moderate validity and is able to predict functional capacity well in chronic heart failure patients with distance results of less 490 meters in their 6MWT.

6MWT distance is found to correlate with the QoL of patients with heart failure. Demers et al. in the Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) study suggested that 6MWT is associated with the symptoms of heart failure. The QoL is the most volatile component compared to the 6MWT and the functional capacity, in their relation to treatment changes in patients with heart failure. Santos et al. in their study showed that 6MWT had a correlation to the QoL of patients with heart failure. The QoL of patients with heart failure decreased significantly based on their functional capacity, and the distance of 6MWT also decreases significantly.

Kudtarkar et al. reported a correlation between the decrease in ejection fraction in systolic heart failure over 6MWT distance and QoL by using the Left Ventricular Dysfunctional-36 score (LVD-36). The drop in ejection fraction in patients with heart failure is in line with the decrease of the 6MWT distance and patient’s QoL.
Two-Minute Walk Test
There are several other walk tests performed as alternatives of 6MWT, such as 2-minute walk test (2MWT), 5-minute walk test, 9-minutes walk test, and 12-minute walk test. Other walk tests are not yet proven to be better than 6MWT, except 2MWT, which is often used as an alternative test in patients who are unable to walk for a long period. However, 2MWT is not validated yet, less sensitive and less accurate in describing of daily activities. In 2015, Bohannon et al. conducted a study in the United States, with participants of mean age 18 to 85 years old performing 2MWT, reporting the average distance of 2MWT of 180.9 meters. A similar finding in 2015 in India by Priya et al. with participants of 20 to 80 years old, the average 2MWT distance was 182.69 meters. Another study by Brooks et al. described that in patients who underwent cardiac surgery, their 2MWT results was related to their QoL in post-surgery and recovery periods.

Psychological Status of Patients with Heart Failure
Psychological status of the patient is one aspect of the QoL that can be assessed with a questionnaire. There are various questionnaires to evaluate the QoL of heart failure patients such as Minnesota Living with Heart Failure (MLHFQ), Kansas City Cardiomyopathy Questionnaire (KCCQ), Left Ventricular Disease Questionnaire (LVDQ), Chronic Heart Failure Questionnaire (CHFQ), and Short Form-36 Health Survey (SF-36). Lane et al. compared four questionnaires (SF-36, MLHFQ, MacNew Heart Disease Health-Related QoL questionnaire, and Seattle Angina Questionnaire) to analyze the QoL of patients with heart failure, and found that MLHFQ is the only questionnaire that had a correlation with NYHA functional status. Morgan et al. conducted a systematic review of 120 studies on the QoL of patients with heart failure since 1996-2005. The study stated that the most frequently used questionnaire was MLHFQ, due to its comprehensive assessment aspect. Garin et al. in 2009 also conducted a meta-analysis of four QoL assessment questionnaires for QoL of heart failure patients (MLHFQ, LVDQ, CHFQ, and KCCQ) and obtained the result that all questionnaires had met the minimum requirements in terms of validity and reliability. Of the four questionnaires, MLHFQ was found out to be the most recommended questionnaire.

In 2013, Garin et al. performed a systematic analysis of seven questionnaires on the QoL of patients with heart failure. The questionnaire used was the Chronic Heart Failure Assessment Tool, the Cardiac Health Profile congestive heart failure (CHPchf), the Chronic Heart Failure Questionnaire (CHFQ), the Kansas City Cardiomyopathy Questionnaire (KCCQ), the Left Ventricular Disease Questionnaire (LVDQ), the Minnesota Living with Heart Failure Questionnaire (MLHFQ), and the Quality of Life in the Severe Heart Failure Questionnaire. The results show that CHFQ, KCCQ and MLHFQ are the questionnaires that have better validity than other questionnaires and are superior compared to other questionnaires. Among the questionnaires used to assess the QoL in heart failure, MLHFQ is the most commonly used.

Research by Hoekstra et al. in 2013 using data from Coordinating Outcomes of Advising and Counseling in Heart Failure (COACH) assessed the relationship of QoL and life expectancy and BNP levels in patients with heart failure. The QoL and life expectancy were evaluated using SF-36, KCCQ and MLHFQ questionnaires, and the result of the study shows that QoL is a factor independent of life expectancy.

Soluble-ST2, Walk Tests and Quality of Life
A 6MWT examination can be used in assessing patients’ QoL and correlates well with the questionnaire-evaluated QoL. Tate et al. in the Beta-Blocker Evaluation of Survival Trial (BEST) study reported a strong association between mortality and patients’ QoL. The assessment of QoL using the San Diego Heart Failure (SDHF) and Minnesota Living with Heart Failure Questionnaire (MLHFQ) found no changes in QoL in relation to the given therapy. Furthermore, poor QoL was found to be associated with higher mortality rates. Rahmani et al. in their study at Hasan Sadikin Hospital, Bandung (2015) reported a correlation between the result of 6MWT and QoL in heart failure patients. A significant relationship was also found between ejection fraction, 6MWT distance and QoL examined by using MLHFQ in patients with heart failure. Felker et al. in 2013 reported the relationship between ST2 and functional capacity as well as QoL of heart failure patients. The study obtained a result of increased levels of ST2 will be associated with reduced distance on the 6MWT and poorer QoL.

SUMMARY
Heart failure is a clinical syndrome caused by structural and/or cardiac functional disorders. This condition increases morbidity, mortality, and healthcare costs. Therefore, a versatile modality to be used in assessing the prognostic, functional capacity and QoL assessment are much needed. ST2
is a biomarker that is able to assess the prognostic and treatment outcome suitably. The higher the ST2 levels, the higher the mortality, morbidity and hospital readmission rates, and ultimately resulting in lower QoL and functional capacity of heart failure patients.

REFERENCES