Research Article

Correlation Between sST2, IL-34 and Mortality in CHF Egyptian Patients

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ABSTRACT

Novel biomarkers such as soluble ST2 (sST2), Interleukin-34 (IL34), some traditional biomarkers as BNP, and TNF-α, could be used in diagnosis and prognosis of patients with chronic heart failure (CHF). This study aimed at evaluating the clinical effect and economic impact values of these above-mentioned biomarkers in CHF patients. 41 CHF stage III patients with LVEF ≤ 40 and thirty healthy control volunteers were recruited and accessed via clinical examination, echocardiography, lipid profile, serum electrolytes, and serum biomarkers. Data showed that, serum levels of the four studied biomarkers were significantly elevated in CHF patient as compared to the control group (P< 0.05). A significant negative correlation was observed between serum levels of these biomarkers and LVEF. A significant positive correlation was observed between CRI-I and CRI-II and total cholesterol, LDL-C, sST2, and IL-34 (P< 0.05). It was found that, sST2 is the most prominent predictor in providing independent and additive prognostic information of mortality (P= 0.043) and the most cost-effective biomarker as compared to EF, IL-34, BNP and TNF-α. Elevated serum levels of these novel and traditional biomarkers may be used as indicator for risk stratification and can also, be applied as independent predictors for the mortality among CHF patients. Using specific and cost-effective biomarker may reduce the numbers of patients requiring echocardiography and may help in early diagnosis that, may help in selecting the evidence-based therapy that, in turn, may modify patient's outcomes, and useful to follow the effectiveness of the treatment.

Keywords: Chronic heart failure; Biomarkers, Soluble ST2; Interleukin-34.

INTRODUCTION

Chronic heart failure (CHF) is the major cause of death specially in the elderly. Its management is shifted toward early interventions and the preservation of quality of life, as well as reducing mortality. [1, 2] The high incidence and prevalence of CHF constitute a major health care burden worldwide. [3] Globally, 2%-17% of CHF patients die during their first admission, a reported 17%-45% rate of mortality one year after first admission. Additionally, one half of the patients die within five years after being diagnosed. [4, 5]

In Egypt, heart failure carries a significant economic burden and estimated at 169 Million $ annually, direct and indirect medical and treatment costs, with average cost of hospitalization in Egypt/day for HF 2300 EGP = 260$. [6] In Egypt, Turk-Adawi K et al., 2018 demonstrated that, the World Health Organization (WHO) reports, estimates that, 46% of deaths are due to CVD. [7] It is in this setting elective intends to assess, manage, and perhaps prevent heart failure (HF) have been investigated. [8] Recently, biomarkers get more attention secondary to their effectiveness in CHF management. Since, they may reveal different biological processes, and essential mechanisms involved in pathogenesis, and mortality. [8, 9] Certainly, the biomarkers implicated must reflect many pathobiological processes involved in HF, such as brain natriuretic peptide (BNP) which already acknowledged in HF guidelines. [10]

Pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-34 (IL-34). TNF-α is an inflammatory cytokine that, has been implicated in HF progression. TNF-α is a mediator of myocardial dysfunction and adverse cardiac remodeling. [11] Furthermore, elevated circulating levels of pro-inflammatory cytokines are associated with increased mortality of HF patients. [12] Soluble ST2 has been identified as a novel biomarker for cardiac stress, fibrosis, and remodeling, [13] was recently included in the 2013 ACC/AHA Guideline for The Management of Heart Failure. ACC/AHA Guideline recommended sST2 a predictive factor for hospitalization and death in CHF patients and as an additive factor for to BNP level in its prognostic value.[14]

These aforementioned information gives a strong evidence about the clinical importance for evaluating the role of these novel and traditional biomarkers in patients with CHF. Therefore, the present study aimed at evaluating the clinical and economical values of some novel cardiac biomarkers such as soluble ST2, IL-34, and some traditional biomarkers as BNP, and TNF-α in patients with CHF.

SUBJECTS AND METHODS

From February 2015 to March 2016 stage III CHF patients were recruited from the Cardiology Department, Tanta University Hospital, Tanta, Egypt. A total of 71 subjects including 41 CHF patients (30 CHF patients were

completed the follow up and 5 patients were lost to follow up; 6 patients were died and their baseline data included in the analysis) taken the traditional treatment for stage III (LVEF ≤ 40%), and 30 healthy control subjects. The inclusion criteria were age > 18 and < 75 years old and, NYHA functional class II–IV with LVEF ≤ 40%. The exclusion criteria were age < 18 or > 75 years, anemic patients, fever, patients with liver or renal dysfunction, diabetic patients, patients with inflammatory diseases, autoimmune disease, cancer and pregnant women were also excluded .

Ethical Approval

All procedures performed in this study involving human participants were approved and in accordance with the ethical standards of ethical committee at College of Pharmacy, Tanta University; and Tanta University Hospital Institutional Review Board research committee. The study was conducted in conformity with the standards of Good Clinical Practices and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Eligible patients were informed of the study's purposes. A signed informed consent was obtained from all study patients.

Study design

The study was a randomized, controlled, parallel, prospective study. All participants were submitted to detailed history, physical examination, measurement of height, weight, and calculation of BMI, and, measurement of heart rate, blood pressure. Heart failure was diagnosed according to patients' history, physical examination, and echocardiogram. LVEF, potassium, sodium, chloride levels, serum sST2, IL-34, BNP, and TNF-α concentrations were measured at enrollment (baseline) and three months after follow-up period.

Biochemical assays

Blood samples were collected into non-heparinized tubes and centrifuged immediately. Serum was separated, coded and stored at −80 °C until analysis. Serum potassium, sodium and, chloride levels were determined colorimetrically. Total cholesterol (TC), triglyceride (TG) were measured using enzymatic colorimetric method and high-density lipoprotein (HDL-C) was determined by precipitation method, using commercially available kits (BioSystems, Spain). Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald formula where LDL-C = [TC − HDL-C − (TGs/5)].
The Atherogenic ratios were calculated as follows:
Castelli's Risk Index (CRI-I) =TC/HDL-C
Castelli's Risk Index (CRI-II) =LDL-C/HDL-C

Biomarker's measurements were carried out using Enzyme-linked immunosorbent assay (ELISA) technique using commercially available kits were used according to the manufacturers' instructions for quantitative assay of serum biomarkers.

Serum soluble ST2 and BNP were measured using (RayBiotech, Inc., Norcross GA, USA). On the other hand, IL-34 and TNF-α were measured according to (Boster Biological Technology, LTD, USA), (eBioscience, USA), respectively.

Cost estimation

Cost estimation for sST2, BNP, IL-34, and TNF-α were calculated using costs for the 96-well plate of 770 $, 570 $, 670 $, and 480 $, respectively. Local laboratory handling charge of 3.5 $, 4 $, 4.5 $, and 3 $, respectively were also added for each sample which gives a total cost of 11.5 $, 10 $, 11.5 $, and 8 $, respectively per sample and the cost for an echocardiogram was assumed value of 22 $ (175 EGP).

Survival tree

Classification and regression tree analysis which allows determination of cut-off values to optimize the performance of the biomarker was used to identify the clinical characteristics of biomarkers that were strongly associated with the death (endpoint). [15] The result of this analysis was represented by terminal nodes which are characterized by a set of predictors and their values. Survival tree model was performed for the overall survival time, from the beginning of the study till occurrence of death or till the end of follow-up period.

Statistical analysis

Data were presented as mean ± SD. The statistical analysis was performed using SPSS® statistical package version 22, SPSS Inc 2013, USA. 95% confidence interval with an alpha error of 0.05 was used. Paired and unpaired student's t-test was used to assess any significant difference between the two groups at baseline and after 12 weeks of follow-up period. Pearson's correlation was used to assess the correlation between measured parameters after the intervention. Univariate Cox Regression survival analysis was used to determine the prognostic value of the biomarkers.

Classification and Regression Tree (CART) analysis was used for determining predictors of death, and 'rpart' package in R is used to build up the CART, to determine the optimal cut-off values for continuous variables.

RESULTS

Characteristics of subjects

Demographic data of all participants which defined as age, sex, and BMI were evaluated. In control and CHF group, there were 24 (80%) and 33 (80.5 %) males, respectively. Mean age and BMI were 54.36 ± 5.42 and 55.97 ± 8.27 years, 27.836 ±3.12 and 27.973 ± 2.4 kg/m2, respectively.

There was no statistically significant difference in terms of age, sex and BMI between the two groups (P= 0.357, 0.959, 0.835, respectively).

Table 1 shows the summarization of all measured parameters for the two groups at baseline and, 12 weeks after the standard care of CHF patients. At baseline and 12 weeks after the standard care, patients with CHF were found to have significantly lower HDL cholesterol ($P < 0.05$) and significantly higher heart rate as compared to the control group ($P < 0.05$).

However, no statistically significant differences were observed as regarding systolic blood pressure, diastolic blood pressure, serum potassium, sodium, and chloride levels, total cholesterol, triglyceride levels, or LDL cholesterol levels between the two studied groups ($P > 0.05$).

As shown in Table 1 & Figure 1, the four studied biomarkers levels in CHF group were significantly higher than in its level in the control group ($P < 0.05$). After three months of standard care, CHF group showed a statistically significant decrease in serum sST2, IL-34, BNP, and serum TNF-α levels comparing to its baseline levels ($P < 0.05$). On the other hand, subjects in the control group showed a non-significant change in the 4 studied biomarkers serum levels comparing to its baseline levels ($P > 0.05$).

Among lipid indices, Castelli's Risk Index (CRI-I) and Castelli's Risk Index (CRI-II), when comparing the data obtained with the patient group and the control group, there was non-statistical significant difference at baseline (4.16±1.16 vs. 3.63±1.27; 2.54±1.67 vs. 2.11 ±1.08, $P > 0.05$, respectively), and after three months follow-up period (3.93±1.32 vs. 3.4±1.0; 2.34 ±1.24 vs. 1.93±0.838, $P > 0.05$, respectively).

During the of follow-up period, 6 patients (14.6%) with chronic HF have died, versus no death cases were reported in the control group. Serum sST2, IL-34, BNP, and TNF-α levels in the died CHF patients' group were significantly higher than CHF patients who still alive (506.19±3.869 vs. 419.95±49.03; $p < 0.05$), (223.83 ±7.52 vs. 195.08±16.38; $p < 0.05$), (1071.9 ±61.07 vs. 852.32±136.05; $p < 0.05$), (142.36±9.4 vs. 115.44±20.01; $p < 0.05$), respectively.

Univariate cox regression survival analysis showed that, all studied four biomarkers were significant predictors for the death. The results of univariate analysis for the predictors of death were significant for elevated sST2 level (HR, 1.478; 95% CI, 1.012 to 2.159; P= 0.043), elevated IL-34 level (HR, 1.381; 95% CI, 1.058 to 1.802; P= 0.017), elevated TNF-α level (HR, 1.267; 95% CI, 1.093 to 1.469; P= 0.002), elevated BNP level (HR, 1.030; 95% CI, 1.008 to 1.052; P= 0.007), EF (HR, 0.633; 95% CI, 0.454 to 0.882; P= 0.007). Univariate Cox Regression survival analysis showed that, the most independent predictor for death in CHF patients was serum sST2.

Table 1: Clinical and biochemical parameters for CHF patients' group and for the control group

Parameters	At Baseline		After 12 weeks of CHF standard care		P-value		
					Baseline	12 weeks	
	Control (n=30)	CHF[a] (n=30)	Control (n=30)	CHF[b] (n=30)	Control vs. CHF[a]	Control vs. CHF[b]	CHF[a] vs. CHF[b]
LVEF (%)	61.1±4.76	33.1±5.42	60.96±5.20	33.85±5.80	0.000*	0.000*	0.033*
Heart rate (beats/min)	84.2±9.24	90.93±10.63	82.9±4.94	88.2±6.52	0.011*	0.001*	0.080
Systolic BP (mm Hg)	118.16±10.54	118.16±15.17	117.83±9.06	120±13.39	1	0.466	0.392
Diastolic BP (mm Hg)	77.66±7.27	76.33±9.99	79.33±6.12	77.33±9.71	0.577	0.345	0.470
Potassium (mEq/l)	4.13±0.23	4.17±0.47	4.17±0.22	4.21±0.47	0.729	0.674	0.492
Sodium (mEq/l)	138.80±2.31	137.70±3.83	138.95±1.80	138.87±3.53	0.185	0.909	0.119
Chloride (mEq/l)	97.93±1.98	96.79±2.84	97.92±1.24	97.01±2.66	0.076	0.093	0.754
TC, (mg/dl)	175.43±50.89	165.38±35.44	166.46±41.56	161.33±40.2	0.378	0.629	0.203
TG, (mg/dl)	124.17±54.27	124.96±42.49	113.40±42.63	122.60±38.2	0.987	0.383	0.723
HDL, (mg/dl)	49.63±7.26	41.13±7.91	49.96±7.39	42.80±9.13	0.000*	0.001*	0.246
LDL, (mg/dl)	100.76±46.81	99.25±36.26	93.82±37.82	94.01±38.77	0.889	0.984	0.118
sST2 (pg/ml)	100.19±9.9	419.95±49.03	99.33±11.11	298.37±84.5	0.000*	0.000*	0.000*
TNF-α (pg/ml)	10.85±2.92	115.44±20.01	10.58±2.04	106.79±16.6	0.000*	0.000*	0.024*
BNP (pg/ml)	77.14±18.91	852.32±136.0	75.57±17.08	818.72±159	0.000*	0.000*	0.028*
IL-34 (pg/ml)	119.95±13.12	195.08±16.38	118.02±12.41	187.14±16.7	0.000*	0.000*	0.001*

Data are presented as mean±SD, CHF [a] = Data for the 30 CHF at baseline; CHF [b] = Data for the 30 CHF after 12 weeks of standard care; LVEF= Left ventricular ejection fraction; BP= Blood pressure; TC= Total cholesterol; TG= Triglycerides; HDL= High-density lipoprotein cholesterol; LDL= Low-density lipoprotein cholesterol; sST2= Soluble ST2; TNFα= Tumor necrosis factor alpha; BNP= B-type natriuretic peptide; IL34= Interleukin 34; pg/ml= picograms per milliliter;
* Statistically significant difference ($P < 0.05$).

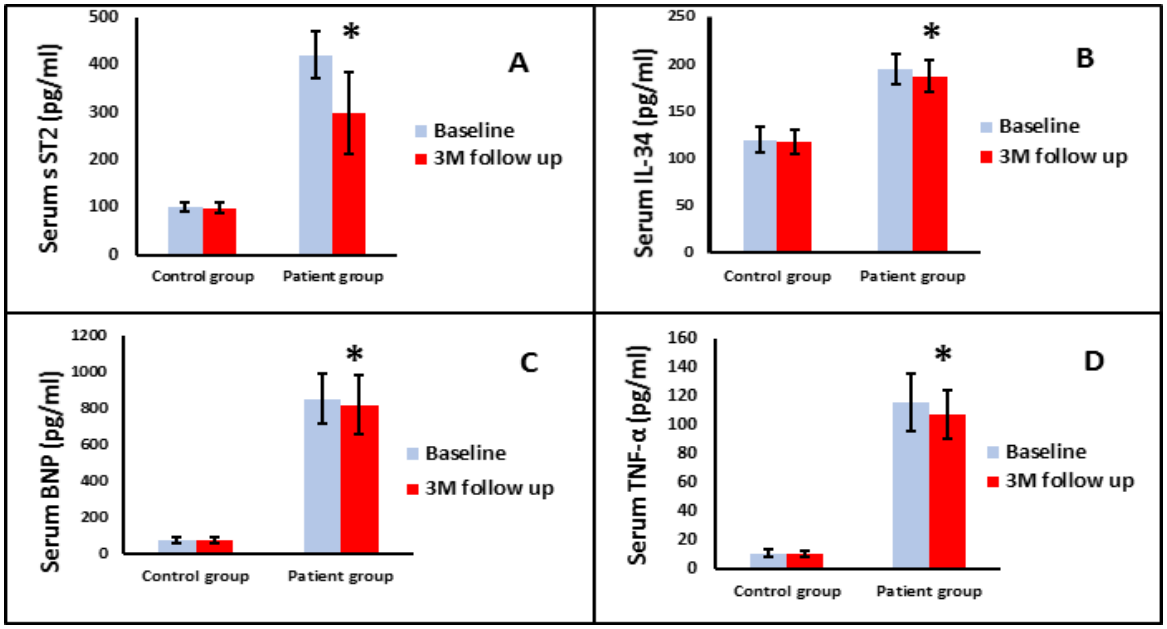

Figure 1: Changes in serum biomarkers by groups at baseline and after three months of follow-up periods

A. Changes in soluble ST2 biomarker; B. Changes in Interleukin-34 (IL-34) biomarker; C. Changes in Brain natriuretic peptide (BNP) biomarker; D. Changes in Tumor necrosis factor-α (TNF-α) biomarker; *Statistically significant difference among studied groups

Correlation between studied variables

Correlation analysis between all measured parameters in CHF group were analyzed after three months of follow-up period. Showed that, there was a significant positive correlation between sST2 and the three other biomarkers IL-34, BNP, and TNF-α (r = 0.894; r = 0.407; r = 0.378, respectively). Furthermore, there was a significant positive correlation between IL-34 and BNP, and TNF-α (r = 0.572; r = 0.454, respectively). A significant positive correlation between BNP and TNF-α was also observed (r = 0.615). On the other hand, sST2, IL-34, BNP, and TNF-α levels were negatively correlated with LVEF (r = - 0.903; r = - 0.955; r = - 0.639; r = - 0.526, respectively). Only IL-34 serum level showed significant positive correlation with LDL-C (r = 0.387). The result of the correlation analysis is shown in Figure 2.

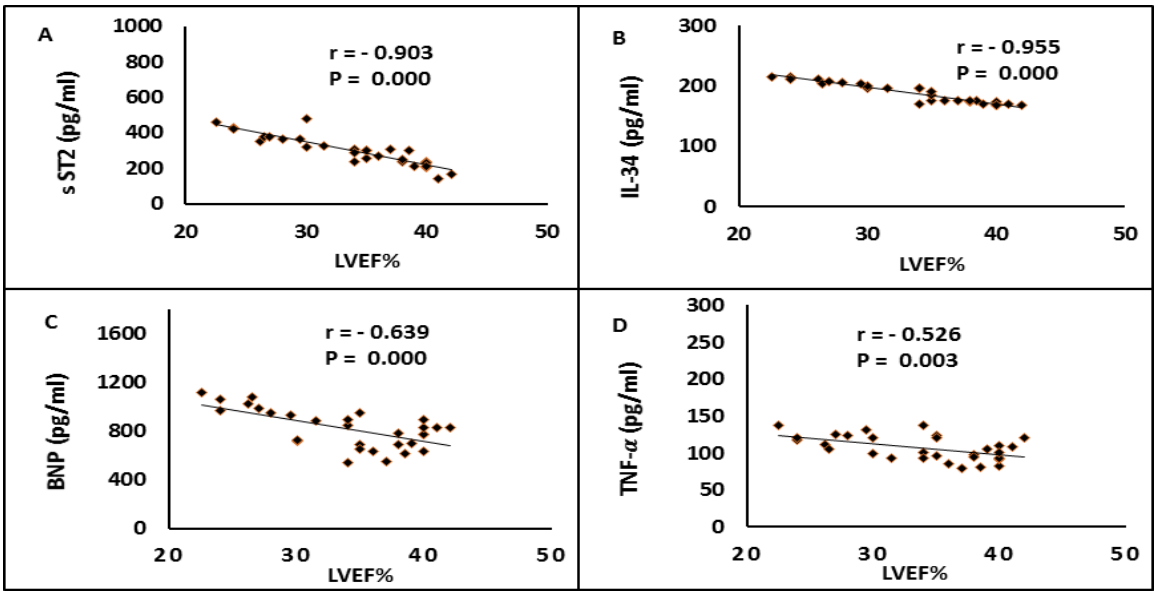

Figure 2: Correlation between measured parameters 12 weeks after standard care of CHF group

A. Soluble ST2 and Left ventricular ejection fraction (LVEF)
B. Interleukin-34 (IL-34) and LVEF
C. B-type natriuretic peptide (BNP) and LVEF
D. Tumor necrosis factor-alpha (TNF-α) and LVEF

When lipid indices in term of CRI-I and CRI-II were correlated with lipid profile and the four studied biomarkers, they showed a positive significant correlation with total cholesterol (r = 0.644; 0.677, respectively), LDL-C (r = 0.803; 0.848, respectively), soluble ST2 (r = 0.402; 0.390, respectively), and IL-34 (r = 0.381; 0.389, respectively). On the other hand, CRI-I, and CRI-II showed a significant negative correlation with HDL-C (r = - 0.605; -0.547, respectively). No significant correlation could be found between CRI-I, and CRI-II and triglycerides, BNP, and TNF-α levels.

Classification and regression tree

The optimal cut-off values according to Olshen survival determined for EF, sST2, BNP, and TNF-α were ≥ 28.5%, < 494.86 pg/ml, < 975.205 pg/ml, and < 130.06 pg/ml, respectively. IL-34, showed two cut-off values, the first cut-off value (IL-34 level was ≥ 219.425 pg/ml) is the worst prognosis indicating death, the second cut-off value (IL-34 level was < 208 pg/ml) indicates the best prognosis.

Determination of the cost-effectiveness biomarker

The effect of each biomarker is assessed by counting the number of correct results obtained when using the cut-off values suggested by Olshen survival tree. As shown in Figure 3, soluble ST2 was found to be the most cost-effective biomarker compared to either IL-34, BNP, TNF-α or EF. Furthermore, soluble ST2 has higher effectiveness and high cost as compared to both BNP and TNF-α. Compared to BNP, the incremental cost-effectiveness ratio (ICER)= [(472-410)/ (40-35)], hence for every correctly predicted death case, we paid extra 12.4$ USA. When compared to TNF-α, the ICER = [(472-328)/ (40-36)], subsequently for every correctly predicted death case, we paid extra 36$ USA.

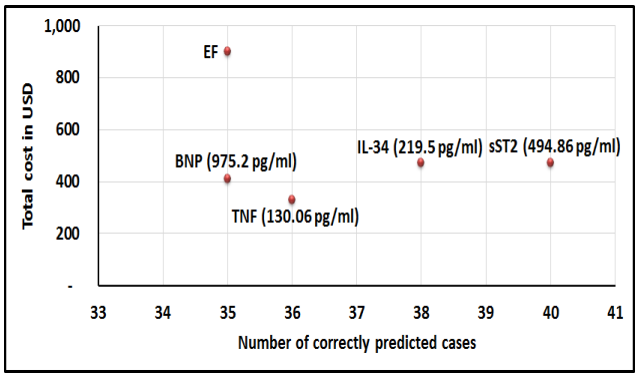

Figure 3: Cost-effective chart illustrates the results of the cost-effective analysis

Soluble ST2 (s ST2); Left ventricular ejection fraction (LVEF); Interleukin-34 (IL-34); B-type natriuretic peptide (BNP); Tumor necrosis factor-alpha (TNF-α); pg/ml= picograms per milliliter.

DISCUSSION

Chronic heart failure (CHF) remains an important clinical entity that has increased in prevalence worldwide as well as a leading cause of cardiovascular morbidity and mortality. [16- 17] The risk stratification of CHF individuals based on clinical criteria and biomarker levels may improve diagnostic and prognostic and probably increase the efficacy of treatment strategy. [18]

In this current study, sST2 and IL-34 biomarkers could be provided a novel and clinically valuable tool in diagnosis and prognosis of CHF patients.

In the current study, there was no significant difference in baseline characteristics in the patient group. Therefore, any change occurs at the end of study follow-up period would be attributed to medication adherence and compliance and will not be related to inter-individual variations.

In this comparative study, we found that, serum levels of sST2, IL-34, BNP, and TNF-α were significantly elevated in CHF patient group as compared to their levels in the control group at baseline and 12 weeks after follow-up period (P < 0.001), these finding confirm the literature based-conclusion. [19- 21]

Our study revealed that, there is statistically significant decrease in sST2, IL-34, BNP, and TNF-α levels as compared to its baseline levels, after the end of the three months follow-up period with a decline in their levels of about (28.95%, P= 0.000; 4.09%, P= 0.001; 3.94%, P= 0.028; 7.49%, P=0.024, respectively). CHF with a decrease in sST2 after 12 weeks had a reduced risk of hospitalization for HF worsening and for cardiovascular causes. [22]

Many studies showed that elevated levels of biomarkers in HF such as BNP, [23- 24] TNF-α [25] and sST2, [19] provide information about differential diagnosis and prognosis of heart failure. Weinberg et al., 2003 reported in PRAISE-2 study that, sST2 levels were significantly higher in severe HF patients as compared to the control subjects. [26] However little is known about the role of IL-34 in HF. Few studies demonstrated that, circulating IL-34 levels showed a significant increase in CHF patients. [27- 28]

The present study demonstrates significant positive correlations between circulating serum levels of sST2, IL-34, BNP, and TNF-α after three months of follow-up period. These aforementioned results are matched with the result obtained by Pérez AV et al., 2010 who demonstrated a significant positive correlation between TNF-α and BNP. [29] Furthermore, these finding agrees with the PRAISE-2 trial that showed a positive correlation between sST2 and BNP levels. [26]

Interestingly, in the present study, was noted a significant negative correlation between LVEF and sST2, IL-34, BNP and TNF-α (r = - 0.903; r = - 0.955; r = - 0.639; r = - 0.526, respectively). This result is accordance with the data obtained by Veena V et al., 2016 & Karakiliç E et al., 2010 who reported a correlation coefficient of r = - 0.445; r = - 0.5, respectively between BNP and LVEF. [23-24] Furthermore, the result is consistent with findings of Yao HC et al., 2015 & Santhanakrishnan R et al., 2012 who

reported a correlation coefficient of r = − 0.324; r= – 0.263, respectively between sST2 and LVEF. [19, 30]

The presence of correlation between these biomarkers' levels and LVEF reflects the degree of severity, left ventricular structural and functional abnormalities in HF. On the other hand, Ansari N et al., 2012 reported that, there is no correlation between TNF-α and LVEF%.[25] Interestingly, TNF-α has showed clinical utility as a biomarker in CHF patients. However, this needs further investigations. Moreover, in the CHF patient group, a statistically significant positive correlation was found between serum IL-34 and LDL-c (r = 0.387), a result that seems in consonance with the data obtained by Li et al., 2012 (r = 0.127). [27]

Recently, Rodondi N et al., 2012; Reddy VS et al., 2015 and Elshazly MB et al., 2015; Pikula A et al., 2015 have found associations between cardiovascular events and low HDL-C and with the TC/HDL-C ratio, respectively. [31-34] Low HDL-C is seeming to be an independent risk factor for cardiovascular disease (CVD). [34]

The current study results agree with these data as CRI-I and CRI-II were showed significant positive correlation with total cholesterol, LDL-C, soluble ST2, and IL-34. On the other hand, lipid indices showed significant negative correlation with HDL-C. No significant correlation could be found between CRI-I, CRI-II and triglycerides, BNP, and TNF-α. Castelli Risk Index (CRI) may be used in the clinical setting for assessing the risk of cardiovascular disease beyond the routinely done lipid profile.

The present study showed that sST2, IL-34, BNP, and TNF-α may be acceptable predictors of mortality risk. BNP have emerged as promising biomarker for CHF diagnosis, prognosis, and treatment. The previous studies concluded that, BNP is a strong independent predictor for cardiovascular mortality and hospitalization in patients with CHF, irrespective to LVEF, NYHA functional class and this matched with results achieved in our study. [12, 35- 37]

Another study reported an association between sST2 and HF severity, where patients with elevated levels of sST2 had an increased risk for death and become conducted for heart transplantation. [38] Gruson et al., 2014 reported that, sST2 was the strongest predictor for death in patients with HF as compared to EF and BNP. In addition, sST2 exhibited a higher risk discrimination power over BNP. [39]

Furthermore, Chang et al., 2014 have demonstrated that, increased expression of IL-34 is usually affected by TNF-α level. [40] Serum IL-34 level may be used as an additional inflammatory marker for diagnosis and prognosis of CHF patients.

Furthermore, Sobczak et al., 2014 confirmed the ability of the single baseline sST2 level to predict adverse outcome at one year in patients with LVEF < 30%.[41]

Till now, more evidences demonstrate that, elevated level of sST2 is correlated with high risk of adverse outcomes including death.

Interestingly, in the present study, Survival classification and regression trees (CART) and Univariate Cox Regression showed that, sST2 (P= 0.043) was the most prominent predictor for providing independent and additive prognostic information for death. Our result is consistent with findings of Yao HC et al., 2015 who reported that, elevated baseline of sST2 level was a significant predictor of CHF death (P< 0.05). [19] sST2 was also, the most cost-effective biomarker compared to EF, IL-34, BNP, and TNF-α. Furthermore, when comparing the incremental cost-effectiveness ratio of sST2 with BNP and TNF-α, we paid extra $12.4 or $36 for every correctly predicted death case respectively.

On the other hand, we suggest also that, IL-34 may be used as an additional inflammatory marker for diagnostic and prognostic purposes for patients with CHF. IL-34 is a strong independent prognostic biomarker for HF related outcomes in this current study population. In accordance with our finding raised inflammatory cytokines levels, which was associated with increased mortality was previously reported. [12]

An attempt was made to establish which important predictor biomarker for mortality among patients with CHF over the 12-weeks follow-up period. This aimed to improving our prognosis approach while screening patients with high risk who need more attention and care.

Study limitations/Recommendations

This study was self-funded and the small sample size was the main study limitation which is not representative of all CHF population. Further larger scale studies are still requiring to get a deeper insight into the inflammatory potential of IL-34 and to better point out the evidence for routine use of sST2 in the clinical evaluation of a patient with CHF.

CONCLUSION

The present study demonstrates that, elevated serum sST2 and IL-34 levels were found to be valuable indicators in risk stratification and to be independent predictors of death in patients with CHF. Using specific and cost-effective biomarker in primary care may reduce the numbers of patients requiring echocardiography and may be help in predicting mortality, aids in early diagnosis that facilitates selecting the evidence-based therapy that could modifies patient's outcomes, and useful to follow the effectiveness of the treatment.

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