Baseline High-Sensitive-Cardiac Troponin I as a Predictor of Fatality in Stable Chronic Heart Failure Patients in Nigeria

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INTRODUCTION

Cardiac troponin I (cTnI) has been proven to be a useful biomarker in patients with chronic heart failure (CHF), and a high-sensitive assay for the same is readily available.[1] These assays can detect cTn I or T in >95% of healthy adults.[2] Cardiac troponins (I or T) are a Class IIa B recommendation for risk stratification in patients with CHF.[3] The significant elevations of serum cTnI in CHF identified in this study could signify the presence of limited, irreversible myocyte injury or alternatively could represent leakage of the cytosolic pool during reversible injury.[4] Therefore, this study sought to determine the usefulness of cTnI in predicting the 6-month HF outcome at the Federal Teaching Hospital, Ido-Ekiti, Nigeria.

METHODS

Patients

Sixty-four consecutive consenting outpatient participants managed for CHF who have clinical and echocardiographic diagnosis of HF (HF with reduced ejection fraction (EF) and HF with preserved EF) and on standard HF regimen were included in the study. Participants with acute myocardial infarction (MI), acute HF, or those with hospitalization for heart failure (HF), has been well studied in developed countries. However, its significance in patients with chronic HF (CHF) in Nigeria and Africa at large remains unknown. 

Methods: This was a hospital-based prospective study. Sixty-four consecutive consenting patients with clinical and echocardiographic evaluation for HF attending cardiology clinic were recruited. They all had resting 12-lead electrocardiogram done. Blood sample for serum hs-cTnI assay (enzyme-linked immunosorbent assay), electrolytes, urea, and creatinine was obtained at recruitment and at 6 months. The participants were followed up monthly for 6 months from baseline to determine the case fatality rate and hospitalization rate. Results: At the end of 6 months, four patients were lost to follow-up. Eight participants died of HF-related cause and had statistically significantly higher mean recruitment serum hs-cTnI levels than the survivors (0.35 ± 0.05 ng/ml vs. 0.23 ± 0.02 ng/ml), P ≤ 0.001. Baseline hs-cTnI ≥0.25 ng/ml was found to be an independent significant prognostic predictor of HF fatality on Cox regression analysis. Conclusions: This study demonstrated that hs-cTnI was predictive of HF fatality in a cohort of patients with CHF in Nigeria. Thus, it may be used to risk stratify patients as a guide to identify those likely to benefit from more aggressive management.

KEYWORDS: Heart failure fatality, high-sensitive-cardiac troponin I, prognostic predictor

ABSTRACT

Background: The prognostic value of high-sensitive-cardiac troponin I (hs-cTnI), a biomarker for heart failure (HF), has been well studied in developed countries. However, its significance in patients with chronic HF (CHF) in Nigeria and Africa at large remains unknown. Methods: This was a hospital-based prospective study. Sixty-four consecutive consenting patients with clinical and echocardiographic evaluation for HF attending cardiology clinic were recruited. They all had resting 12-lead electrocardiogram done. Blood sample for serum hs-cTnI assay (enzyme-linked immunosorbent assay), electrolytes, urea, and creatinine was obtained at recruitment and at 6 months. The participants were followed up monthly for 6 months from baseline to determine the case fatality rate and hospitalization rate. Results: At the end of 6 months, four patients were lost to follow-up. Eight participants died of HF-related cause and had statistically significantly higher mean recruitment serum hs-cTnI levels than the survivors (0.35 ± 0.05 ng/ml vs. 0.23 ± 0.02 ng/ml), P ≤ 0.001. Baseline hs-cTnI ≥0.25 ng/ml was found to be an independent significant prognostic predictor of HF fatality on Cox regression analysis. Conclusions: This study demonstrated that hs-cTnI was predictive of HF fatality in a cohort of patients with CHF in Nigeria. Thus, it may be used to risk stratify patients as a guide to identify those likely to benefit from more aggressive management.

Study protocol

At recruitment, clinical evaluation for diagnosis of HF was performed, and each patient’s severity of symptoms was determined using the New York Heart Association functional classification.[3] Clinical diagnosis of HF was based on the Framingham’s criteria.[6] Drug history was recorded. Blood samples were obtained from the peripheral vein, and serum levels of electrolytes, urea, and creatinine alongside high-sensitive-cTnI (hs-cTnI) were measured. Echocardiography was performed on the same day. Resting 12-lead electrocardiography was done to exclude patients with acute renal disease with an estimated glomerular filtration rate of <15 ml/min/1.73 m², and those who were uncertain about willingness to adhere to clinic visits were excluded from the study. Informed consent was obtained from each participant prior to enrollment, and the protocol was approved by the Research Ethics Committee of the institution.

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with MI. In this study, CHF patients were defined as those who had never been hospitalized as well as those who had a previous history of hospitalization, whether recent or remote, but currently not presenting with any symptoms that would necessitate hospital admission. The lower limit of detection of the assay was 0.03 ng/ml; all patients had values higher than this.\textsuperscript{[2]} The main end point was hospitalization or death related to HF during the course of follow-up.

**Measurements of biomarker**

The serum cTnI was assayed using human cTnI enzyme-linked immunosorbent assay (ELISA) kit by Accubind\textsuperscript{®} microwells ELISA kits (Monobind Inc., Lake Forest California, USA). This kit allows for in vitro quantitative determination of human cTnI concentration in the serum.\textsuperscript{[2,7]}

**Method of data analysis**

Receiver operating characteristic (ROC) curve was drawn to determine the cutoff value of serum cTnI that had the best sensitivity and specificity for predicting mortality. A Kaplan–Meier survival curve was constructed for survival studies. Confidence level was set at 95%, and level of significance was set at $P < 0.05$. The required sample size was determined using the statistical formula estimation for longitudinal studies.\textsuperscript{[8]}

**RESULTS**

Nearly 79\% of the survivors had hs-cTnI $<0.25$ ng/ml, whereas 75\% of the nonsurvivors had values $>0.25$ ng/ml. Both functional class and baseline troponin were significantly different in both groups as shown in Table 1a.

The most common etiology of HF in our cohorts was hypertension and most patients were on standard HF regimen as shown in Tables 1b and c, respectively.

There was no significant difference in troponin levels of patients at baseline and after 6 months of follow-up as shown in Table 2.

At the end of the follow-up, as clearly shown in Table 3, eight (13.3\%) patients had died due to HF-related causes and ten (16.7\%) were hospitalized for worsening of their HF symptoms. The nonsurvivors had significantly raised baseline hs-cTnI in comparison to the survivors; however, no difference in hospitalization rate was noted.

Figure 1 shows the ROC curve, and examining the coordinates of the curve on Table 4, the best combination of sensitivity and specificity is at an hs-cTnI value of 0.25 ng/ml because its confidence interval excludes 0.5; thus, it can be postulated that hs-cTnI levels adequately predict mortality at 0.25 ng/ml as seen in this study.

**Table 1a: Characteristics at baseline in sixty patients with chronic heart failure according to cardiac death**

| Variables                  | Survivors ($n=52$) | Nonsurvivors ($n=8$) | Total ($n=60$) | $P$   |
|----------------------------|--------------------|----------------------|----------------|------|
| Age (<65/≥65 years)        | 23/29              | 3/5                  | 26/34          | 0.720 |
| Gender (male/female)       | 28/24              | 6/2                  | 34/26          | 0.459 |
| Mean BMI (kg/m$^2$)        | 24.5±5.1           | 21.4±2.8             | 24.1±4.9       | 0.021*|
| Mean WC (cm)               | 86.7±11.1          | 82.1±10.8            | 86.1±11.1      | 0.297 |
| Ejection fraction (<35/≥35\%) | 19/33              | 3/5                  | 22/38          | 0.732 |
| Mean eGFR (ml/min/1.73 m$^2$) | 59.9±20.0         | 47.4±12.0            | 58.2±19.5      | 0.027*|
| NYHA Class (I-II/III-IV)   | 48/4               | 1/7                  | 49/11          | <0.001*|
| Prolonged QTc (yes/no)     | 32/20              | 4/4                  | 36/24          | 0.816 |
| Baseline troponin (<0.25/≥0.25 ng/ml) | 41/11             | 2/6                  | 43/17          | 0.006*|

*Statistically significant. BMI=Body mass index, WC=Waist Circumference, eGFR=Estimated glomerular filtration rate, NYHA=New York Heart Association

**Table 1b: Etiology of chronic heart failure according to cardiac death**

| Variables                  | Survivors ($n=52$), n (%) | Nonsurvivors ($n=8$), n (%) | Total ($n=60$), n (%) | $P$   |
|----------------------------|---------------------------|-----------------------------|-----------------------|------|
| Hypertension               | 24 (46.2)                | 5 (62.5)                    | 29 (48.3)             | 0.778 |
| Dilated cardiomyopathy     | 19 (36.5)                | 3 (37.5)                    | 22 (36.7)             |       |
| Rheumatic heart disease    | 5 (9.6)                  | 0 (0.0)                     | 5 (8.3)               |       |
| HIV cardiomyopathy         | 2 (3.8)                  | 0 (0.0)                     | 2 (3.3)               |       |
| Peripartal cardiomyopathy  | 2 (3.8)                  | 0 (0.0)                     | 2 (3.3)               |       |
| HIV=Human immunodeficiency virus

**Table 1c: Medication use according to cardiac death**

| Variables                  | Survivors ($n=52$) | Nonsurvivors ($n=8$) | Total ($n=60$) | $P$   |
|----------------------------|--------------------|----------------------|----------------|------|
| Furosemide (yes/no)        | 50/2               | 8/0                  | 58/2           | 0.573 |
| ACEIs/ARBs (yes/no)        | 51/1               | 8/0                  | 59/1           | 0.692 |
| Spironolactone (yes/no)    | 50/2               | 8/0                  | 58/2           | 0.573 |
| Beta blockers (yes/no)     | 15/37              | 3/5                  | 18/42          | 0.619 |
| Digoxin (yes/no)           | 17/35              | 5/3                  | 22/38          | 0.103 |
| Warfarin (yes/no)          | 34/18              | 5/3                  | 39/21          | 0.873 |

ACEIs=Angiotensin-converting enzyme inhibitors, ARBs=Angiotensin receptor blockers
Table 2: Troponin levels of patients at baseline and after 6 months of follow-up

| Variables                        | mean±SD (ng/ml) | T   | P   |
|----------------------------------|-----------------|-----|-----|
| Cardiac troponin at baseline     | 0.25±0.06       | 1.62| 0.10|
| Cardiac troponin at 6 months     | 0.23±0.07       |     |     |

Table 3: Association between baseline cardiac troponin levels and outcome among patients

| Variable                      | Mean±SD (ng/ml) | n  | T   | P   |
|-------------------------------|-----------------|----|-----|-----|
| Hospitalization for worsening heart failure | 0.25±0.03 | 10 | 1.02 | 0.310 |
| No                            | 0.23±0.06       | 50 |     |     |
| Outcome after 6 months of follow-up |          |    |     |     |
| Dead                          | 0.35±0.05       | 8  | 12.36 | <0.001* |
| Alive                         | 0.23±0.02       | 52 |     |     |

*Statistically significant. SD=Standard deviation

Table 4: Coordinates of the receiver operator characteristic curve

| Cardiac troponin I cutoff value | Sensitivity | Specificity |
|---------------------------------|-------------|-------------|
| 0.000                            | 1.000       | 1.000       |
| 0.150                            | 1.000       | 0.846       |
| 0.250                            | 0.750       | 0.212       |
| 0.350                            | 0.750       | 0.135       |
| 0.450                            | 0.750       | 0.096       |
| 0.550                            | 0.500       | 0.038       |
| 0.700                            | 0.375       | 0.038       |
| 0.850                            | 0.125       | 0.038       |
| 1.000                            | 0.000       | 0.000       |

On bivariate analysis as shown in Table 5, the survival times were significantly reduced in patients with baseline hs-cTnI ≥0.25 ng/ml. Similar findings are also shown in Table 6 on Cox regression analysis of time to death after 6-month follow-up on prognostic variables as shown in Table 6.

Kaplan–Meier survival curves were constructed according to the survival functions as depicted in Figure 2, and it showed that hs-cTnI ≥0.25 ng/ml had poorer cumulative survival.

**Discussion**

A number of clinical and laboratory parameters help identify HF patients with a potentially poorer outcome. hs-cTnI has been proven to be a useful biomarker in determining the prognosis of patients with CHF.[1] A wide range of hs-cTnI levels (0.026–0.5 ng/ml) have been reported among HF patients in different studies.[9] There are multiple assays for hs-cTnI in contrast to cTnT, in which only one platform exists.[10,11] The limit of detection of the assay used in this study was 0.03 ng/ml. All the study participants had detectable troponin, which confirms the high-sensitive nature of the assay.[2]

The mean hs-cTnI values of patients both at baseline and at 6 months in this study were higher than that in a similar study done among stable outpatients with nonischemic CHF patients in Japan.[1] The reason could be due to the different kits that were used Accu-bind (Monobind Inc., Lake Forest California, USA) vs. Siemens (Laboratory Diagnostics. 511 Benedict Avenue. 10591-8000 Tarrytown, NY, USA) and the characteristics of the population tested.

The hospitalization rate of 16.7% as seen in this study is comparable to the rate of 13.9% found among patients with HF in a prospective study by Watanabe et al.[12] which included stable CHF patients who had never been hospitalized as well as those who had a previous history of hospitalization, whether recent or remote.

The 6-month case fatality of 13.3% in this study as shown in Table 3 can be comparable with 11.4% found by Logeart et al.[13] among Caucasians in a derivative study to determine the predictors of outcome of HF after a 6-month follow-up. It is, however, lower than 17.8% reported by Damasceno et al.[14] in a study of patients with HF in sub-Saharan Africa who were also followed up for 6 months. This might probably be due to the fact that the latter comprises of acute HF patients who are expected to have a higher risk of adverse events than our own patients who are stable and some of whom had never been hospitalized before. In this study, it was found that the patients that died had statistically significant elevations in their baseline hs-cTnI compared with those that were alive and completed the follow-up. This is comparable to a similar study by Tsutamoto et al.[1] who found that hs-cTnI was significantly higher at baseline in nonsurvivors than in survivors. These findings suggest that measurement of cTnI using high-sensitive assays maybe useful for predicting prognosis and risk stratification even in patients with CHF who seem to be clinically stable.[1] This has been consistent in all the available related studies till date, which clearly
Table 5: Log rank tests from bivariate survival analysis of time to death after 6-month follow-up on variables

| Variable          | Survival time in days (time to death or follow-up) mean±SD | n  | Log rank $\chi^2$ | $P$  |
|-------------------|------------------------------------------------------------|----|------------------|-----|
| Gender            |                                                            |    |                  |     |
| Male              | 166.9±40.7                                                 | 34 | 0.73             | 0.47|
| Female            | 174.2±34.5                                                 | 26 |                  |     |
| Age (years)       |                                                            |    |                  |     |
| <65               | 171.0±39.0                                                 | 26 | 0.14             | 0.89|
| ≥65               | 164.6±37.8                                                 | 34 |                  |     |
| Ejection fraction |                                                            |    |                  |     |
| <35               | 174.3±30.6                                                 | 22 | 0.77             | 0.44|
| ≥35               | 166.1±43.6                                                 | 38 |                  |     |
| NYHA class        |                                                            |    |                  |     |
| 1 and 2           | 174.1±55.7                                                 | 40 | 19.78            | <0.001*|
| 3 and 4           | 142.7±57.3                                                 | 20 |                  |     |
| Prolonged QTc interval |                                                      |    |                  |     |
| Yes               | 172.1±37.6                                                 | 36 | 0.45             | 0.65|
| No                | 167.5±39.2                                                 | 24 |                  |     |
| Baseline troponin |                                                            |    |                  |     |
| <0.25             | 175.2±34.6                                                 | 44 | 7.65             | 0.019*|
| ≥0.25             | 160.6±47.7                                                 | 16 |                  |     |

*Statistically significant. SD=Standard deviation, NYHA=New York Heart Association

Table 6: Cox regression of time to death after 6-month follow-up on prognostic variables

| Variable          | HR   | 95% CI HR | $P$  |
|-------------------|------|-----------|-----|
| Age (years)       |      |           |     |
| <65               | 0.61 | 0.14-2.67 | 0.508|
| ≥65 (ref)         | 1.00 |           |     |
| NYHA class        |      |           |     |
| 1 and 2           | 0.38 | 0.04-0.69 | 0.036*|
| 3 and 4 (ref)     | 1.00 |           |     |
| Prolonged QTc interval |      |           |     |
| Yes               | 0.47 | 0.11-2.12 | 0.327|
| No (ref)          | 1.00 |           |     |
| Baseline troponin |      |           |     |
| <0.25             | 0.27 | 0.02-0.87 | 0.025*|
| ≥0.25 (ref)       | 1.00 |           |     |

*Statistically significant. NYHA=New York Heart Association, HR=Hazard ratio, CI=Confidence interval, ref=Reference category

demonstrates the prognostic value of different types of cardiac troponins in CHF patients.\textsuperscript{[9]}

In a related study, an increase in hs-cTnI seen after 6 months of follow-up was found to be an independent significant prognostic predictor on multivariate analysis after a follow-up of 4.25 years.\textsuperscript{[1]} Sato et al.\textsuperscript{[15]} also further corroborated that serial increase in cTnT is important in identifying HF patients with adverse prognosis. However, the prognostic role of troponin on mortality beyond 6 months of follow-up could not be ascertained in our study; a longer duration of follow-up may have shown this. Kaplan–Meier survival curves showed that cumulative survival was reduced in patients with hs-cTnI ≥0.25 ng/ml. Similar findings were found in a related study.\textsuperscript{[1]}

**Study limitations**

This was a hospital-based study.

The prognostic role of troponin on mortality beyond 6 months of follow-up could not be ascertained among HF patients included in this study. Further studies will be needed to determine this.

**Conclusions**

Overall, in this study, it was found that elevated hs-cTnI was an independent predictor of mortality in HF patients within 6 months of follow-up regardless of the underlying aetiology. In addition, consequent upon the statistically significant elevations seen in hs-cTnI of nonsurvivors in comparison with survivors in this study, hs-cTnI level may be regarded as a novel marker of fatality in Nigerian patients with CHF.
Such strata of patients may benefit from more aggressive management. Our findings further add to the existing risk stratification data for short-term risk of death in ambulatory patients with CHF in our environment.

**Recommendations**

First, hs-cTnI should be included as part of the workup for ambulatory CHF patients for risk stratification. In addition, patients with elevated hs-cTnI in spite of apparent clinical stability should be considered as having a higher risk of mortality and therefore should be closely monitored in specialized HF clinics and placed on guideline-directed medical therapy. Future studies to assess the effect of medical therapy adjustments on changes in hs-cTnI levels are warranted. Furthermore, a multicentric study, enrolling larger number of patients with longer duration of follow-up, is required in order to establish the prognostic significance of hs-cTnI in Nigerian HF patients and help standardize our care of HF patients in line with best international practices.

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Nil.

**Conflicts of interest**

There are no conflicts of interest.

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