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High-sensitive cardiac troponin hs-TnT levels in sudden death related to atherosclerotic coronary artery disease

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ABSTRACT

INTRODUCTION: Ischemic heart disease (IHD) related to atherosclerotic coronary artery disease (CAD) is one of the most prevalent causes of death in Europe. Also post-mortem evaluation of IHD remains a challenge because of possible non-specific autopsy finding in some autopsy cases, especially in early myocardial ischemia. High-sensitive troponin T (hs-TnT) is used today in clinical practice as the “gold standard” to diagnose the myocardial ischemia, and might also be applied as an ancillary tool for post-mortem evaluation.

PURPOSE: The goal of this study is to evaluate the diagnostic value of post-mortem serum hs-TnT assay in cases of sudden death related to IHD. We will also investigate the influence of cardiopulmonary resuscitation (CPR) attempts on post-mortem hs-TnT levels.

METHODS: The hs-TnT values in serum were retrospectively analysed in 85 autopsy data (2012-2015, University Center of Legal Medicine in Lausanne). 52 cases with clinical history and morphological results suggesting cardiac ischemia were included in the study group (mean age 53.5; age range 34-75), 33 in the control group (mean age 40.4; age range 15-69). The group’s statistical comparison was performed using logistic regression model.

RESULTS: Our study showed a significant non-linear association between hs-TnT serum values and post-mortem diagnosis of sudden deaths related to IHD (p -value 0.005). The shape of the relationship is showing that the probability of death due to IHD increases quickly with a light level of hs-TnT (maximum around 90ng/L), then decreases slightly while remaining at high in values. No significant difference in the hs-TnT serum values was found between the CPR and the non-CPR cases (p -value 0.304).

CONCLUSION: The measurement of Hs-TnT serum values might be considered as an ancillary tool for the evaluation of death related to IHD, while taking necessary precautions in the interpretation of the results.

Key words: High-sensitive cardiac troponin hs-TnT, sudden death, myocardial ischemia

INTRODUCTION

One of the most prevalent causes of death in Europe is ischemic heart disease (IHD) related to atherosclerotic coronary artery disease (CAD) [1]. In clinical medicine, the diagnosis of IHD is based on clinical symptoms, electrocardiogram and biochemical markers. Post-mortem evaluation is more complicated as the anamnesis and diagnostic method are limited. Moreover, autopsy findings are not always specific, particularly if arrhythmias follow an acute coronary, event after a long post-mortem period or after a resuscitation attempt [2]. Therefore, forensic pathologists have turned towards the use of cardiac biomarkers, a biochemical method initially developed in clinical medicine, in an attempt to facilitate diagnosis of post-mortem IHD. These markers can become useful when morphological results are not conclusive at the autopsy. However, interpreting them in a post-mortem evaluation still remains a challenge.

Among cardiac biomarkers, troponin is the most frequently used in clinical practice. This derives from the fact that cardiac troponins are more sensitive and specific markers of cardiomyocyte injury than creatine kinase (CK), its MB isoenzyme (CK-MB) and myoglobin [3]. The troponin is a protein complex that plays an important role in the regulation of the excitation-contraction phenomenon of cardiomyocytes. When an acute myocardial infarction occurs, cTnT and cTnI, both major cTn complex proteins, will be released in the blood flow. They will be detectable and quantifiable in the peripheral blood, indicating the myocardial traumatism.

The clinical measurements of troponin appeared first in the mid-2000s and established itself as the “gold standard” for myocardial infarction diagnosis [4]. It was then replaced by the high-sensitive troponin T (hs-TnT) assay, using the same immunoassay method with new antibodies more sensitive to the cardiac troponin [5]. For the diagnosis of an acute myocardial infarction (AMI), two dosages are needed for the protein to reach a measurable level. The time-lapse between these two dosages using the old method was from 6 to 9 hours, and decreased to 3 hours with the hs-TnT assay allowing for a precious time saving in terms of diagnosis [4, 5]. Hs-TnT assay is today the “gold standard” for AMI diagnosis. It is systematically used in the clinical practice as a specific marker for cardiac necrosis and became a full-fledged criteria in the European Heart Journal’s approved definition of the myocardial infarction [6]. In clinical evaluation, the probability of an AMI will depend of the

level of hs-TnT in serum [4, 5]. It is however important to notice that the increase of the level of troponin reflects the myocardial cells' necrosis and is thus not specific to any particular disease [5].

Many clinical cardiac biomarkers were tested in post-mortem examination [7-21] . The post-mortem experimental use of the classical troponin assay started early already in the 2000s. Yet the added value of its studies outcomes in forensic diagnosis always remained controversial. There are also different opinions about the effects of cardiopulmonary resuscitation (CPR) on the increase of troponin level. Some authors suggested that the potential cardiac trauma could affect the release of troponin [22], however the scientific literature reports mainly that the effects on troponin level were non-significant in post-mortem autopsies [9, 19, 23].

To date, only one study has been driven using the new high-sensitive assay on postmortem serum and pericardial fluid by González-Herrera et al. in 2016 [24]. It was stated that serum levels do not show any correlation with any cause of death. Significant differences of troponin levels were however noticed in pericardial liquid level. The authors showed that low hs-cTnT levels in pericardial fluid allowed the exclusion of the heart damage, and concluded that the accuracy of this new method and its results is calling for an appropriate interpretation and a need for re-evaluation.

Then, although many studies published scientific writings concerning the evaluation of biomarkers in post-mortem cases, literature remains rather uncertain about the post-mortem diagnosis value of hs-cTnT. Points of view emerged that troponin could be useful as an ancillary diagnostic tool to identify the cause of death, while one must remain cautious when interpreting the results. Therefore, this new biomarker requires more post-mortem studies in order to understand the diagnostic use in autopsy practice. The goal of our study is to evaluate the diagnostic value of post-mortem hs-TnT's assays in serum. We will focus on IHD's sudden death cases related to atherosclerotic coronary artery disease, with or without morphological signs of cardiac ischemia. The influence of CPR attempts on post-mortem hs-TnT levels will also be evaluated.

MATERIAL AND METHODS

Cases

The retrospective study was performed on autopsy data retrieved from the database of autopsies conducted by the University Center of Legal Medicine in Lausanne (CURML) between 2012 and 2015. The estimated post-mortem period did not exceed 72 hours. Study cases were selected on the basis of clinical history and/or morphological results suggesting the death from cardiac ischemia. This included cases with acute coronary thrombosis with or without signs of myocardial necrosis, and cases with coronary stenosis > 75%, without another detectable cause of death. Both cases of advanced cadaveric deterioration and postoperative death were excluded from the study, as well as a person who had previously refused in a written document to give his/her corporal substance for research use.

Control cases included cases of violent death (hanging, gunshot, etc.) with no cardiovascular pathology at the morphological examination, and without clinical story or autopsy findings suggesting any cardiovascular disease.

In each case, the examination of the heart involved macroscopical and histological evaluations. The histological examination was performed including at least five different topographic locations; namely left ventricle (anterior, lateral, posterior), interventricular septum and lateral wall of the right ventricle. The sections were routinely stained with haematoxylin–eosin, followed in selected cases by immunochemistry (fibronectin and C5b-9). The body and heart weights were noted for each body.

This study received the ethical approval by the Cantonal Commission for the Ethics of Human Research (CER-VD).

Biochemical analyses

Serum was collected during the autopsy. It was derived from a blood sample, centrifuged immediately after its collection. It was stored at -20°C until the time of analysis. Levels of post-mortem serum cardiac troponin T were measured with hs-TnT reagents by electrochemiluminescence immunoassay (ECLIA). Results were expressed in nanograms per liter [18]. Cases with the troponin values higher than $10'000\text{ng/l}$ were excluded as considered as excessively altered and outside the analytical range.

Statistical analyses

Categorical data were summarized by their frequencies and percentages. For the age, the body weight and the hearth weight, the summary was given by their mean (sd) and range. Univariate logistic regression was performed to assess the association between each predictor and the outcome “cause of death” (reported as Odds-Ratios (OR) and p-values). The functional form of the relationship between the continuous variables (hs-TnT level, age, body weight and hearth weight) and the probability of death due to IHD was checked using a fractional polynomial model. The linearity assumption was confirmed except for the troponin T (hs-TnT) level (Figure 3). The level of the troponin T (hs-TnT) was then coded into three categories (≤ 12 coded by 0, $[13-2250]$ coded by 1 and ≥ 2251 coded by 2) to assess the risk of death due to IHD when being in the categories 1 or 2 compared to the reference category 0.

RESULTS

A total of 85 cases (68 males and 17 females) were selected, 52 for the study group (age range 34-75) and 33 for the control group (age range 15-69). Among those from the study group, acute thrombosis was found in 19 cases, 23 cases presented a severe atherosclerosis ($>75\%$ of luminal stenosis) without coronary thrombosis, 8 cases presented a moderate atherosclerosis (50-75% of luminal stenosis) and signs of myocardial ischemia, and finally two cases presented only signs of myocardial ischemia.

The troponin levels varied between 3 and 9687 ng/l. Complementary characteristics about cases and control are summarized in Table 1.

Statistical results

No statistical correlation with hs-TnT values were found considering the time period between the death and the serum sample analysis measured for both cases and controls (Fig 1). There were also no significant differences between hs-TnT values of reanimated and non-reanimated cases from the control group (p -value 0.304; Fig. 2). Finally, no significant differences in value were observed between the hs-TnT cases with and without signs of

microscopic ischemia (p -value 0.634). Therefore, we were able to select our samples of cases and controls without taking those characteristics into account.

Therefore, using the previous results from the case-control pool, we found no significant difference in hs-TnT values between cases with morphological signs of ischemia and controls (p -value 0.345). There were also no significant differences in hs-TnT values between cases without signs of microscopic ischemia and controls (p -value 0.840). We also noticed that the increase of hs-TnT levels in elderly patients with heavy heart weight, in presence of atherosclerosis or of cardiovascular symptoms before death (prodrome), was significantly associated with a high probability of being included in the “study case” category.

We observed however that our study demonstrates a non-linear significant association between hs-TnT serum values and the presence of IHD (p -value 0.005, Fig. 3). The shape of the relationship is showing that the probability of death due to IHD increases quickly with a light level of hs-TnT (maximum around 90ng/L), then decreases slightly while remaining at a high level.

DISCUSSION

The use of clinical medicine biomarkers is a challenge for the forensic pathologists. While their interpretation is relatively established in a clinical context, it is not far the case for post-mortem use. The actual challenge when using post-mortem biomarkers lies in the interpretation of these values that need to be adapted to the specific biomarkers and the context of post mortem evaluation.

The values of hs-TnT observed in our study and their interpretation are different from the ones seen in clinical medicine. The results of our study demonstrate that the hs-TnT level increases frequently in post-mortem studies, both in cases and/or controls. This fact is often mentioned in the literature. Thus, regardless of the technique used (TnI, TnT, hs-TnT), levels of cardiac biomarkers, either in case or control studies, are usually significantly higher than the reference range for living patients [7, 20, 21, 24, 25]. The reason for this upsurge is unclear; haemolysis and autolysis were suggested [25, 26], as well as non-specific lesions and "invisible" infarction due to hypoxia of the myocardium during terminal agony [20, 21]. It

seems thus clear that the threshold level used clinically (ante-mortem) could be meaningless or questionable in the post-mortem context.

Our study revealed a non-linear significant association between hs-TnT serum values and the presence of IHD. This result seems not to be in accordance with the findings of the González-Herrera et al. study, reporting no correlation between the different causes of death and the serum levels of cTnT [24]. We observed an increased probability of mortality in the IHD group related to a peak value of hs-TnT (around 90 ng/L). Above this value, the probability does not increase anymore, on the contrary to the use of hs-TnT in clinical medicine [4]. Moreover, beyond this limit, we observed a slight decrease of the probability of IHD. Therefore, according to the results of our study, very high values of hs-TnT (as 2500 ng/L) are not correlated with a higher probability of IHD death. We observed also that the correlation between the increase of hs-TnT and the probability of IHD death was higher in older victims, with an increased weight of heart, and atherosclerosis and cardiovascular symptoms before death (prodromes). Those results are not surprising and are in accordance with literature, clinical data as well as with physiopathology of the myocardial ischemia [27].

Furthermore, our results underline the importance of the autopsy investigations and demonstrate that the measurement of cardiac biomarkers should be considered only as an additionally diagnostic tool. Indeed, no differences between the hs-TnT values were found in cases with and without morphological signs of ischemia and controls. This could be also explained by the fact that in coronary thrombosis cases, sudden death could occur before the increase of hs-TnT.

Our study showed that the attempt of a CPR does not seem to lead to a significant increase of post-mortem hs-TnT. These findings are in accordance with the results found in scientific literature [9, 19, 23] concerning the “classical” troponine assay. Also, clinical studies about the hs-TnT support that CPR may lead to a non-negligible increase of troponin in survivors [22]. No other evaluation was reported to this day for post-mortem evaluation of hs-TnT in reanimated cases.

The hs-TnT levels found in our study were measured in serum samples. According to the literature, post-mortem troponine levels often depend on sampling sites. It was reported that pericardial fluid would be the most representative sample site (more direct “salting out” of

troponin from the myocardium to the sample site due to the proximity of each other) [20, 21, 25]. The troponin in pericardial fluid seems to show a better negative predictive value for post-mortem investigations than serum. This has been raised regarding the classical troponin assay [13, 15, 16], as well as in the single post-mortem evaluation of hs-TnT assay [24]. We consider that the evaluation of the hs-TnT levels in pericardial fluid for the post-mortem diagnosis of IHD would be interesting in future studies.

Finally, it should also be underlined that, in a clinical context, it has recently been demonstrated that the specificity of hs-TnT for acute myocardial infarction is very low as the increased values are observed in myocardial damage of any origin [28, 29]. The increase of troponin levels indicates the presence of cardiomyocytes damage, but not the mechanisms. For example, other causes than IHD, cardiac or not, can lead to an increase of hs-TnT; arrhythmias, cardiac contusion, myocarditis, pericarditis, different kinds of heart failure, chronic renal failure, cerebrovascular accidents, acute pulmonary embolism, chronic obstructive pulmonary disease (COPD), drug intoxication and other acute non-cardiac critical illness [5, 24, 28]. In our study such cases were excluded regarding the clinical history and morphological results. We consider however that the interpretation of a rise of the hs-TnT should be very careful and that again more studies with larger samples could be useful.

Study limitation

The essential limitation of this study is related to post-mortem context, impossible to be ruled out. This could lead to a biased increase of hs-TnT as reported for other post-mortem studies. The number of cases and moreover the number of controls included in this study is relatively small to obtain a better significance of the results. Therefore, we suggest performing more studies to further our knowledge in this interesting topic.

CONCLUSION

Our study showed a non-linear significant association between hs-TnT serum values and the presence of IHD at the cause of death, with a different profile compared to the clinical field (peak around 90ng/L, then slight decrease of the probability). It was however impossible to determine a cut-off value as for living patients in clinical medicine, probably because of the

non-specific and unpredictable rise of hs-TnT due to post-mortem alterations. No significant difference of hs-TnT serum values was found between the CPR and the non-CPR cases

It seems reasonable to state that hs-TnT assay in serum can be considered as an additional tool for the evaluation of death related to IHD, while remaining cautious when interpreting the results. However, the use of this new high-sensitive assay requires more studies, especially with a focus on the pericardial fluid.

Legends

Fig. 1; Description of the variability of hs-TnT level in serum according to the post-mortem period in the 2 groups; cases and controls.

Fig. 2; Distribution of hs-TnT level in serum for control-cases reanimated versus not reanimated. No significant difference were noticed (two sample Wilcoxon test).

Fig. 3; Fig(a): fitted non-linear relation-ship between the hs-TnT level in serum and the predicted(logit)+residuals for death related to IHD. Fig(b): The probability of death related to IHD according to the hs-TnT level in serum. Fig(c): the same as Fig (a) with the zoom for the hs-TnT level in serum between [3-2250]. Fig(d): the same as Fig(b) with the zoom for the hs-TnT level in serum between [3-2250]. The two red vertical lines correspond to the hs-TnT level in serum=12 and 2250. Blue dashed horizontal line in Fig(d) indicate that the probability of death related to IHD was upper to 50% for the hs-TnT level in serum between [3-2250].

Table 1; Summary of data relating the main characteristics including the number, the age, the body weight, the heart weight and the hs-TnT values for cases and controls. The association between each characteristic and the outcome measured using the OR and associated *p-value*.

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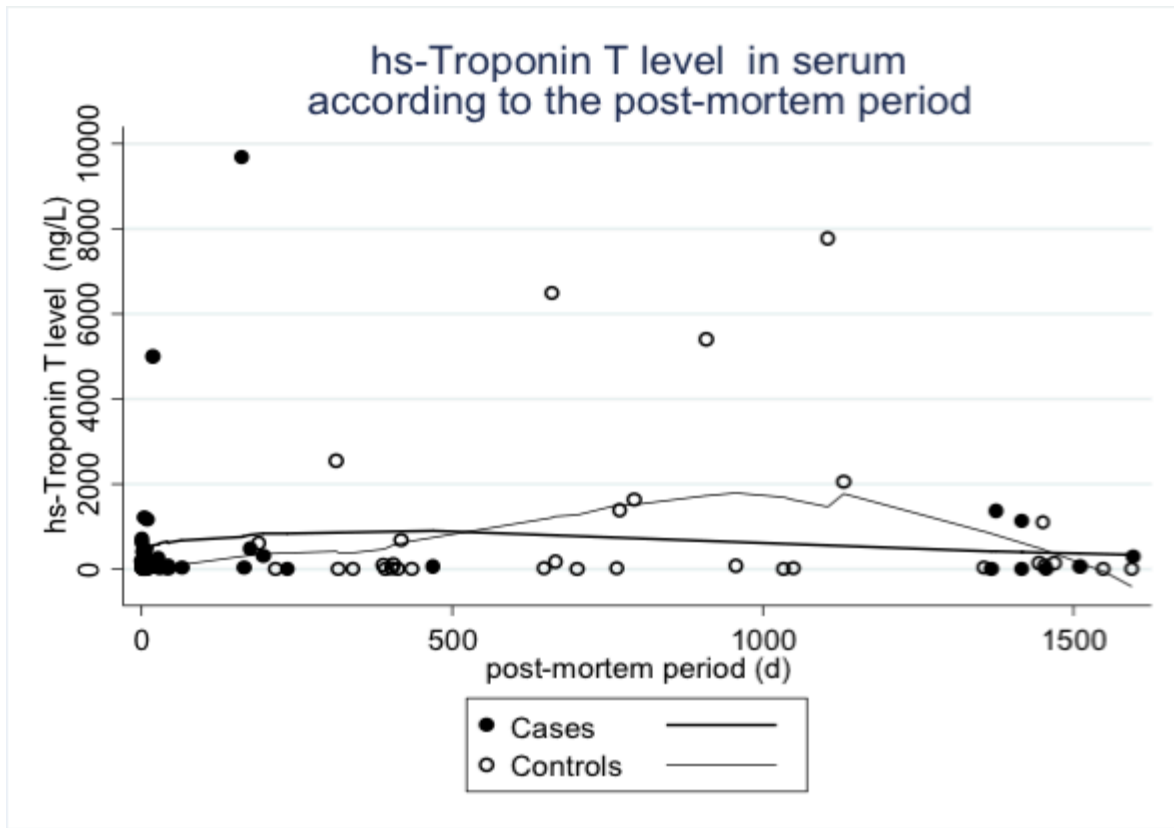


Fig.1 Description of the variability of hs-TnT level in serum (ng/L) according to the post-mortem period (day) in the two groups; cases and controls.

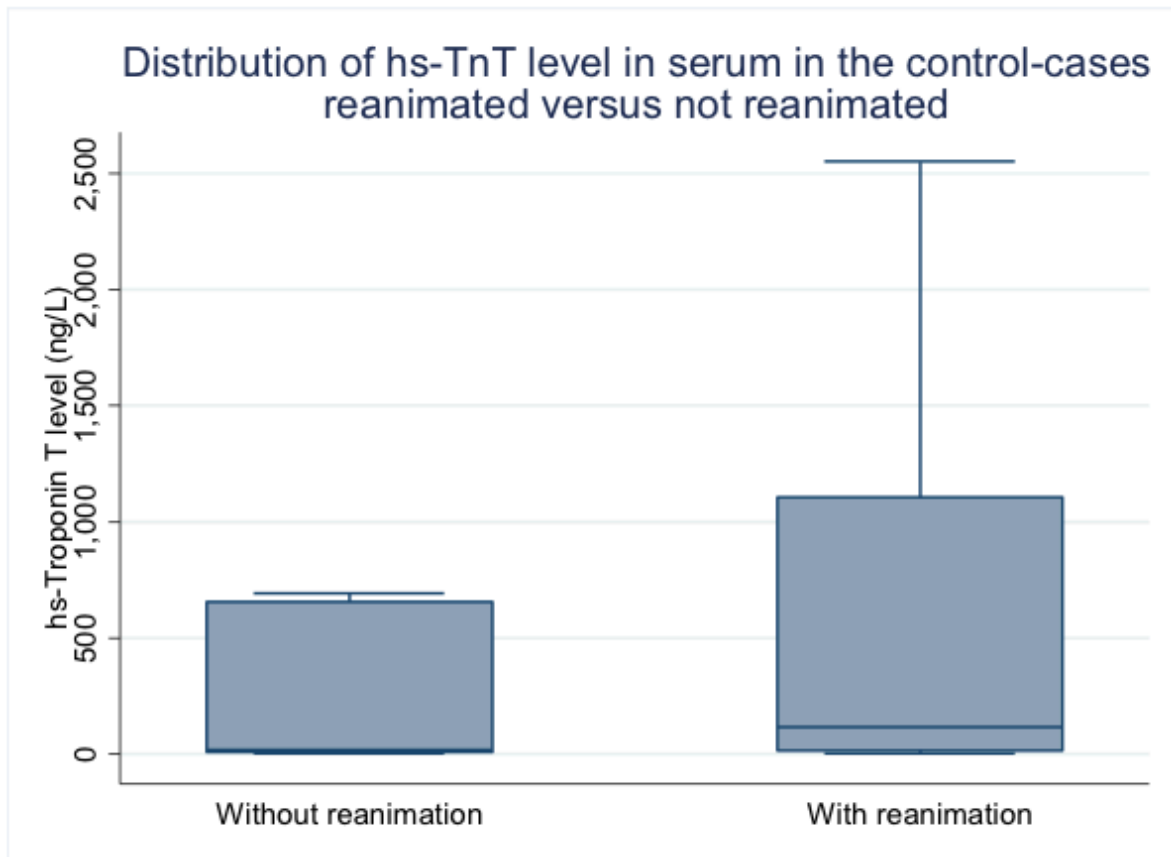


Fig. 2 Distribution of hs-TnT level in serum (ng/L) for control-cases reanimated versus not reanimated. No significant difference were noticed (two sample Wilcoxon test).

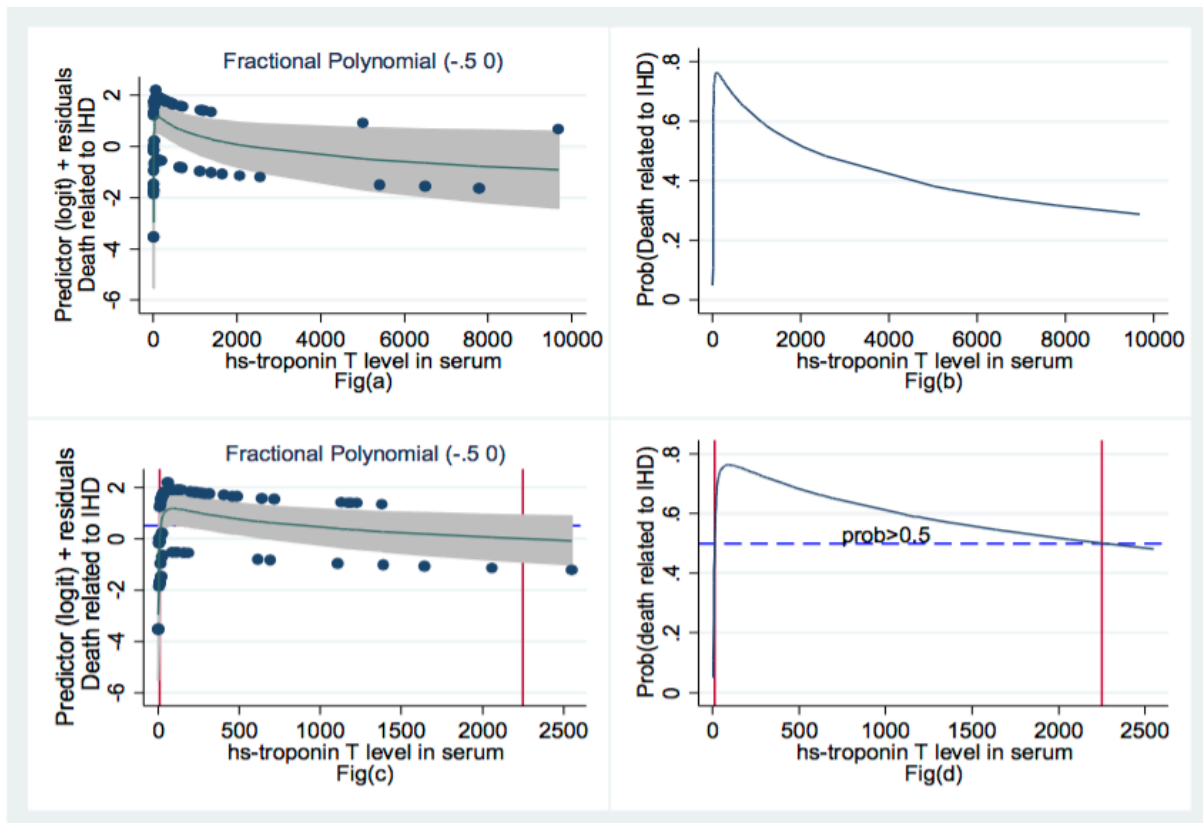


Fig. 3 Fig(a): fitted non linear relation-ship between the hs-TnT level in serum (ng/L) and the predicted(logit)+residuals for death related to IHD. Fig(b): The probability of death related to IHD according to the hs-TnT level in serum (ng/L). Fig(c): the same as Fig(a) with the zoom for the hs-TnT level in serum (ng/L) between [3-2250]. Fig(d): the same as Fig(b) with the zoom for the hs-TnT level in serum (ng/L) between [3-2250]. The two red vertical lines correspond to the hs-TnT level in serum=12 and 2250 (ng/L). Blue dashed horizontal line in Fig(d) indicate that the probability of death related to IHD was upper to 50% for the hs-TnT level in serum between [3-2250].

Variable	Cases N (%)	Controls N (%)	Odd ratio	<i>p</i> - <i>value</i>
N (%)	52 (61.2)	33(38.8)		
Sex Male, n (%)	45 (86.5)	23 (69.7)	2.79	0.06
Age [y] Mean (sd) min-max	53.54 (9.5) 34-75	40.42 (14.1) 15-69	1.09	<0.0001
Body weight [kg] Mean (sd) min-max	82.12 (14.9) 55-140	75.36 (18) 43-121	1.03	0.07
Heart weight [g] mean (sd) min-max	477.50 (108.9) 285-790	350.76 (90.8) 175-565	1.01	<0.0001
Hs-TnT[ng/L] ≤12[ref]	4(7.7)	10(30.3)	-	
[13-2250]	46(88.5)	19(57.6)	6.05	0.005
>2250	2(3.8)	2(3.8)	1.25	0.83

Table 1 Summary of data relating the main characteristics including the number, the age, the body weight, the heart weight and the hs-TnT values for cases and controls. The association between each characteristic and the outcome measured using the OR and associated *p*-value.