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PERFORMANCE OF HIGH SENSITIVE TROPONIN T ASSAY IN EARLY DIAGNOSIS OF MYOCARDIAL INFARCTION

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ABSTRACT

Background: High sensitive troponin T assay (hs-Tn T assay) is one of the most important tests in clinical laboratories. It is commonly used as a diagnostic test for the acute myocardial infarction. However, many health clinics have doubted the ability of this assay to rule in or out myocardial infarction. It is important to review available studies to determine the possibility of using this assay in the early diagnosis of myocardial infarction. This systematic review was conducted to evaluate the performance of this assay at presentation and compare it with conventional troponin assay. **Method:** PubMed, Cochrane databases, EBSCO, AccessMedicine and Google scholar were searched to find out the studies that evaluate the performance of the high sensitive troponin T assay and compare it to conventional troponin assay. As results of using the inclusion and exclusion criteria and The QUADAS tool 4 studies were selected. All of these studies assess the performance of high sensitive troponin T assay (hs-Tn T assay) and compare it with conventional troponin assay. **Results:** The high sensitive troponin T assay has better performance than conventional troponin assay in early diagnosis of MI. It is extremely sensitive assay can help the physician to recognize the acute myocardial infarction early before other complication can develop. Based on the extracted data the mean sensitivity of this assay in 4 studies at presentation is 83.5% while the specificity is 76.8%. **Conclusion:** Both conventional troponin assay and high sensitive troponin T assay has good accuracy. However, the hs-Tn T assay has better sensitivity at presentation and can improve the early diagnosis of myocardial infarction.

KEYWORDS: AMI: acute myocardial Infarction **cTnT**: cardiac troponin T **ED:** emergency Department **hs-Tn T assay:** high-sensitivity cardiac troponin T, **MI:** myocardial infarction.

INTRODUCTION

Troponins are a group of structural proteins found in different body muscles like skeletal and heart muscle (Twerenbold et al., 2011). There are three different types of troponin which are Troponin I, T and C (Twerenbold et al., 2011). This protein has become one of the most important cardiac biomarkers nowadays. Presence of this protein in blood at significant level indicates damage in heart cells (Twerenbold et al., 2011). Myocardial Infarction (MI) is the most common cause of heart muscle damage (Twerenbold et al., 2011). Around 15-20 thousand per million come to the emergency department with symptoms of MI in Europe and United States (Twerenbold et al., 2011). Thus, the early diagnosis of myocardial infarction has become a critical issue worldwide. There are many cardiac enzymes that can help to diagnose MI like CK-MB, troponin, and myoglobin (Mayo Clinic staff, 2016). However, according to the American College of Cardiology (ACC) and European Society of Cardiology (ESC) guidelines the only enzyme that should be measured in case of suspected MI is troponin (Zafari, 2017).

The troponin assay is one of most important test that used to diagnose the myocardial infarction. It is commonly used to distinguish Acute Myocardial Infarction (AMI) from Non-Acute Myocardial Infraction (Non- AMI) (Twerenbold et al., 2011). Since introducing the troponin assay in 1990 it became the main test for diagnosis any Coronary Artery Disease (Willeit et al, 2017). However, the major problem of conventional troponin assay is deficient sensitivity in early few hours of acute myocardial infarction. Thus, it gives a false negative result in early few hours of heart muscle damage. As results, the High sensitive troponin assay was introduced in clinical practice. It was first used in clinical practices in Europe, Canada, and Australia in 2010 and it was defined by its ability to measure troponin protein in blood circulation (Sherwood et al, 2014). This assay has the ability to detect a very low concentration of troponin in the bloodstream and it can

detect very small damage of heart muscle after the symptoms occur (Sherwood et al, 2014). Thus, it can be used to early rule in or rule out the myocardial infarction. According to many studies the High Sensitive Troponin Assay gives accurate results and can help and improve the diagnosis MI patients (Sherwood et all, 2014). In addition to this, two larges prospective multicentre studies found that the high sensitive troponin assay has high sensitivity and accuracy compared to conventional troponin assay (Sherwood et all, 2014). The ability of this assay in the early detection of MI make it the most important test in cardiac profile.

Despite the advantages of using this accurate assay in the diagnosis the acute coronary syndrome, there are different opinions on the specificity of this assay on the diagnosis of myocardial infarction (Sherwood et al, 2014). There are many skepticisms of using this assay to rule in/out AMI worldwide. It has been shown that troponin can be released in many health conditions other than MI (Beck, 2014). These conditions include trauma, chronic kidney disease and pulmonary embolism (Beck, 2014). According to Westermann et all 2017 in the 45%-65% patients who show high troponin level there are no evidence that they have acute MI. Moreover, the reference range of troponin changes from one group of the population to another (Mody et al., 2016). Thus, the main problem is how we can establish the reference range of each population (Mody et al., 2016). Recent cohort study includes 12000 participants found that the reference range of High sensitive troponin T assay is affected by Age, sex, and race (Giannitsis et al, 2009). Furthermore, using the elevated high sensitive troponin value is not enough to diagnose MI (Mody et al., 2016). This is because of low specificity of troponin that elevated in myocardial damage without identifying the cause of this elevation. Moreover, according to (Sherwood et al, 2014) the level of troponin is not detectable in the patient with stable coronary artery disease. This result led to reducing the validity of this test. However, the elevation of troponin in healthy individual put the validity of the diagnosis of MI based on results of hs-Tn T assay at risk (Mody et al., 2016). Common elevation of troponin in diabetes, heart failure, and chronic kidney disease is considered a big challenge of routine use of high sensitive troponin T assay. Moreover, one of the most significant issue of using this assay is inability of many physicians to interrupt the result of this assay (Mody et al., 2016). Since the majority of patients who came in ED with chest pain do not have the myocardial ischemia (Anderson JL, 2007). It is important to evaluate the performance of the high sensitive troponin T assay which can differentiate AMI from Non-AMI. Thus, there is high need to such this systematic review to clarify some issues related to hs-Tn T assay and to make a clear picture about its performance at presentation. The aim of this systematic review is to evaluate the performance of the high sensitive troponin T assay in early diagnosis of AMI and comparing its performance to conventional troponin assay using the available recent studies. This systematic review will provide clear picture about sensitivity and specificity of the high sensitive troponin T assay and it will evaluate its performance at presentation and finally it will compare its performance to conventional troponin assay. This will be achieved by searching about studies that evaluate the performance of this assay in different databases and exclude that do not evaluate its performance directly or do not compare its performance to conventional assay.

METHOD

To investigate the performance of high sensitive troponin T assay (hs-Tn T assay) preliminary search was conducted on 22 November 2017 using the following data resources: PubMed, Cochrane databases, EBSCO, AccessMedicine and Google Scholar to find out studies that evaluate the performance of the high sensitive troponin T assay and compare it with conventional troponin assay. As results of preliminary search more than 3000 articles related to hs-Tn assay were found. After that, the search was specified by using following keywords: high sensitive troponin assay, specificity and sensitivity of high sensitive troponin T assay, the efficiency of the high sensitive troponin to diagnose myocardial infarction, high sensitive troponin assay and comparison of high sensitive and conventional troponin assays. By using these terms, the number of articles reduced to less than 20 articles. For the purpose of quality and specificity of the search the studies were excluded if there are Systematic review studies, opinion or text studies and if there were published before 2010. Also, they were excluded if they do not compare high sensitive troponin assay with conventional assay directly. To avoid any factors that can affect the quality of the search and to increase its efficiency we filtered the articles that we obtained using PubMed search filter, Cochrane databases search filter and EMBASE search filter. As result of using inclusion and exclusion criteria and other methods of filtering the number of articles reduced to 10. We screened the 10 articles and we selected the best 4 articles based on the number of participants, outcomes and the quality of the method that has been used. All of these articles study the high sensitive troponin T assay against different type of conventional troponin assay and examine the performance of each using sensitivity, specificity, positive predictive value and negative predictive value.

To make sure that the studies are strong enough we critiqued them using The QUADAS critical appraisal tools. The types of checklists that are used are experimental studies checklist, cohort studies checklist and diagnostic study checklist. By using these critical appraisal tools, the strength and the weakness points of each article were identified and. As result of using The QUADAS tool critical, it has been seen that 4 studies are at high quality and they met all required criteria and they do not have bias. The selected articles were fully reviewed by 2 students (Issa Alnjauidi, Ibrahim Alhabsi).

The process of identifying the articles is clearly summarized in figure 1.

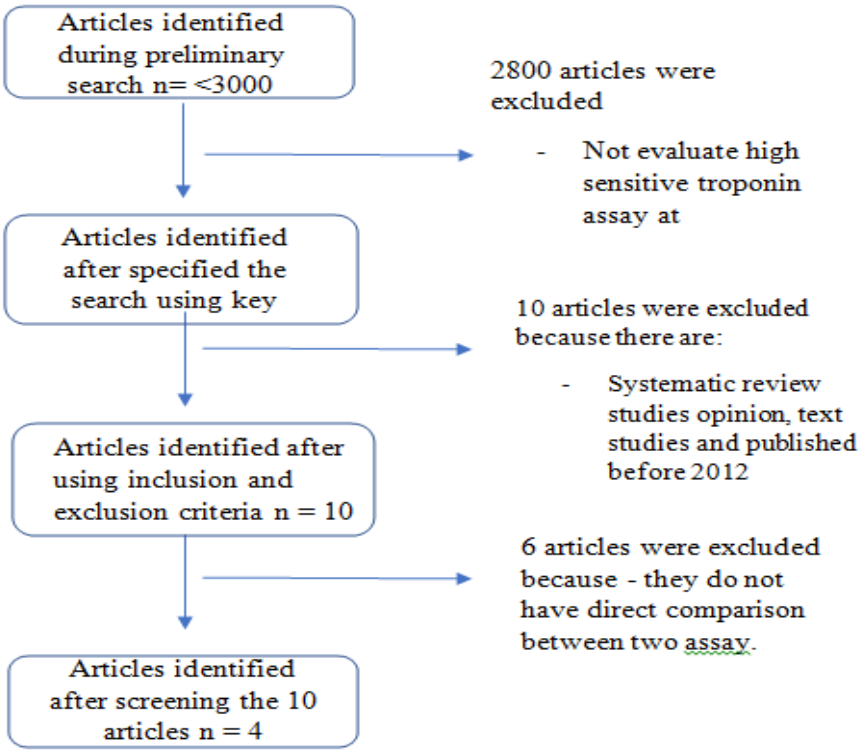


Figure 1: Process of identifying the articles that evaluate the performance of the high sensitive troponin T assay at presentation.

The PICO question of this systematic review is: Can the high sensitive troponin T Assay be used in early diagnosis of AMI compared to conventional troponin assay? Patients: AMI patients, Intervention: hs-Tn T assay, Comparison: conventional troponin assay and Outcome: the high sensitive troponin improve diagnosis of myocardial infarction.

RESULTS

Target populations and outcomes definition

As result of the deep search 4 articles were identified. All of these articles evaluate the performance of the high sensitive troponin T assay through the sensitivity and specificity of and compare it to the conventional troponin assay. All of these studies enrolled patients who came to the emergency department with symptoms suggest AMI like chest discomfort. The troponin level in those patients was measured at presentation and after 3 or 6 hours using the high sensitive troponin T assay and conventional troponin assay. Most of the cut off of these assays were corresponding to 99 percentile of the population. Th final diagnosis of AMI was confirmed by electrocardiography (ECG), angiographically, clinical history and other parameters. The definition of the acute myocardial infarction in selected studies was according to the 2007 or 2012 ESC guideline (European society of cardiology) and ACC guideline (American College of Cardiology). Table 1 summarizes the characteristics of the articles that have been identified.

Table 1: Summary of studies that studied the high sensitive troponin T assay and h conventional troponin assay.

Study	Participants, no.	Year	Design	Centre(s)	Timing of troponin measurement hs-Tn and conventional assay	Outcome, no. (%)
Isikscan. et al	527	2017	Observational comparative study	Single center: Turkey	Within first 6 hour	MI 41
Yonathan et al. 2011	317	2011	Observational comparative study	Single center: France	At presentation and 3-9 h later if needed.	MI 32
Sally et al	1479	2011	Observational comparative study	Single center: New Zealand	At presentation and 6–24 h later	MI110
Body et al., 2011	703	2011	Cohort study	Single center USA	At presentation after3 and hours.	MI 108
MI = myocardial infarction.						

Assessment of the quality of selected studies

To assess the quality of selected studies the QUADAS tool was used. This tool is designed to evaluate the diagnostic accuracy of studies and to identify the risk of bias. It is commonly used to evaluate the studies for systematic review. This tool showed that the selected articles are at good quality. The summary of the results that are identified as results of using the QUADAS tools are fully described in the table 2.

Table 2: The result of assessment of studies that study the performance of high sensitive troponin T assay and conventional troponin assay using QUADAS tool.

Study	Representative sample	Prober time of tests?	Acceptable selection criteria	Acceptable reference standard to classify patients	Reference standard for all patients	Reference standard results blinded?	Acceptable reference standard for assay?	Index test results blinded?	Uninterpretable results reported ?	Withdrawals explained?
Isikscan et all 2017	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Freund et al	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes
Sally J Aldous	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
(Body et al., 2011)	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes

Diagnostic performance of the hs-Tn T assay at presentation

All the articles that we identified report the sensitivity and specificity of the hs-TnT assay and compare them with the conventional troponin. The cut-offs that have been used in these were corresponding to 99 percentile of the population. Based on the extracted data Sally J et all et all included 1479 patients and they found that the sensitivity of hs-Tn T assay is 83.6% and the specificity is 83.8% at 0.14ug/L while Freund et all included 137 patients and they found that its sensitivity is 93% and the specificity is 82% at same cu-off. In other hand the Isikscan et all included 527 patients and and they found that sensitivity is 60.49% while the specificity is 67.42% at less than 0.015(ug/L). The final study which was done by Body et al found that the sensitivity is 84.4% and specificity is 84% at less than 0.014 (ug/L). The Table2 and figure 2 summarize the finding with another parameter of comparison.

Diagnostic performance of the conventional troponin assay at presentation

Different assay and cut-off points have been used to study the conventional troponin assay. Sally J Aldous et al found that the sensitivity of conventional troponin assay at 0.01 (ug/L) cut-off is 74.5% while the specificity was 90.5%. In other hand the freund et al found that its sensitivity at 0.14 (ug/L) cut-off value is 71% while the specificity was 97%. Isikscan et all found that the sensitivity of conventional troponin at less than 0.059(ug/L) cut-off is 47.13% while the specificity was 76.12%. Finally, Body et al found that its sensitivity at cut- off 10 ng/l is 79% while its specificity is 94%. The table 4 and figure 3 summarize the finding with other parameters of comparison.

Table 3: Summarize of the finding of the high sensitive troponin T assay at presentation.

Study	assay	Cut – off	Sensitivity	Specificity	PPV	NPV
Isikscan et al	Roche Diagnostic	0.015(ug/L)	60.49%	67.42%	45.8%	78.9%
Freund et al	Roche diagnostic	0.014 (ug/L)	93%	82%	47%	99%
Sally Jet al	Troponin T hs Elecsy Roche Diagnostics	0.014(ug/L)	83.6%	83.8%	71.9%	91.2%
Body et al.	hs-Tn T 2010 Roche diagnostics assay.	0.014(ug/L)	85.4%	82.4 %	52.4%	91.1 %

PPV: positive predictive value
NPV: Negative predictive value

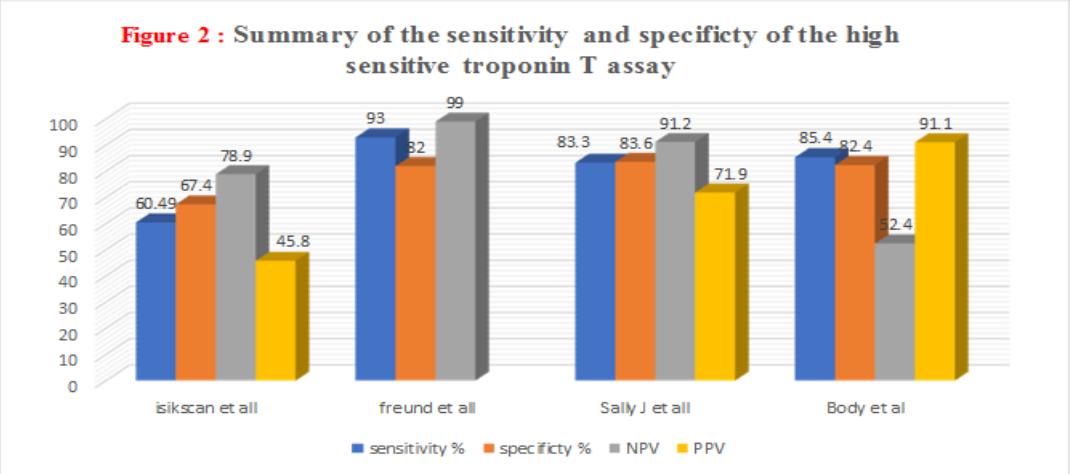
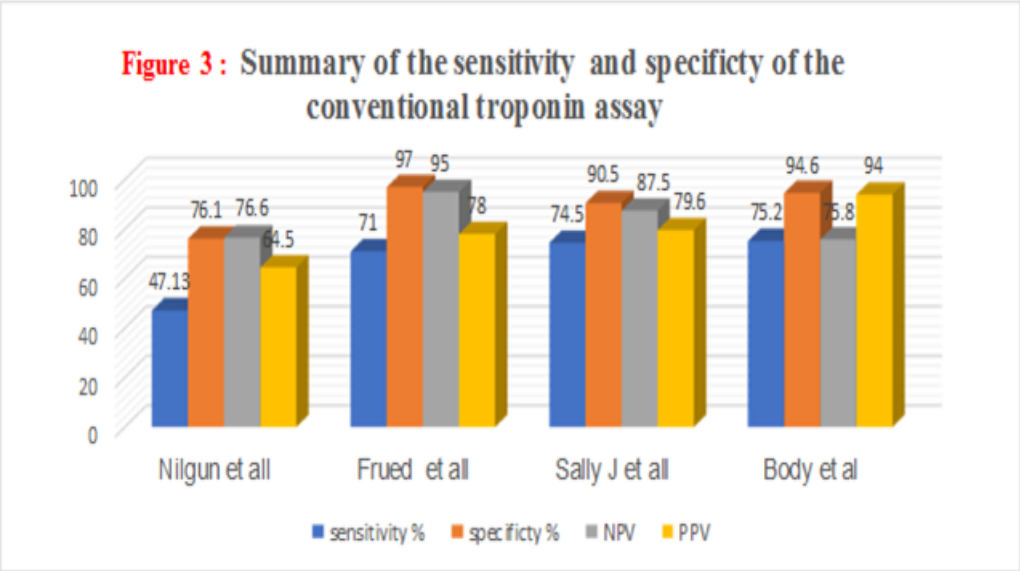


Table 4: Summarize of the finding of the conventional troponin assay at presentation.

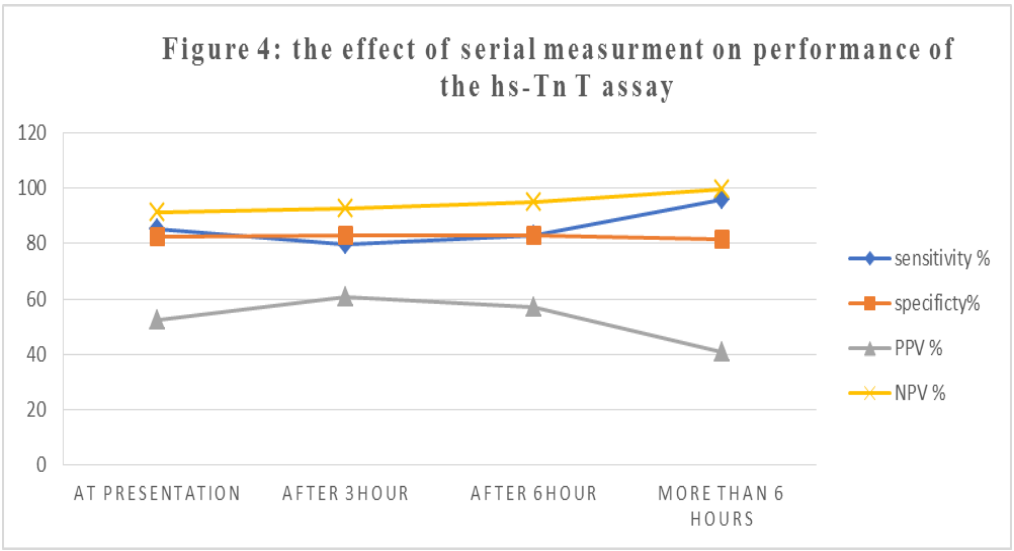
Study	assay	Cut – off	sensitivity	specificity	PPV	NPV
Isikscan et all	Triage conventional troponin	0.059 (ug/L)	47.13%	76.12%	46.5%	76.6%
Freund et all	Siemens healthcare diagnosis	0.14 (ug/L)	71%	97%	78%	95%
Sally J et all	Troponin T STAT Roche Elecsys 2010 system.	0.01 (ug/L)	62.7	95.5%	87.3%	83.8%
Body et al	Roche troponin T [fourth generation]	10 ng/l	75.2 %	94.6 %	75.8%	94 %

PPV: positive predictive value
NPV: Negative predictive value



Effect of serial measurement of troponin T on the accuracy of hs-Tn T assay

According to the finding of the Body et al., 2011 the accuracy of high sensitive troponin T assay is affected by serial measurement of troponin. This study found that the sensitivity and specificity of this assay increased in the second measurement than the first measurement. In addition to this they found that absolute measurement of troponin helps to differentiate the AMI from other cause of troponin elevation. The findings is summarized in figure4. These findings are supported by another study in this systematic review which done by isikscan et all who conclude that rising and/or falling of troponin due to serial measurement can help to distinguish non-ischemic pathophysiology from AMI.



Effect of the renal function test on the performance of high sensitive troponin assay

According to Freund et al 2011 study that is included in this systematic review it has been shown that eGFR influence the performance of the high sensitive troponin assay. Low eGFR can increase the level of troponin. Thus, it affects the results of hs-Tn T assay that is usually used to diagnose cardiac damage.

Troponin elevation in patients without Acute myocardial infarction

According to the results of 4 studies it has been shown that troponin level can be elevated in many conditions other than AMI. These conditions include apoptosis, stress, heart failures, chronic kidney renal disease, and sepsis. Sally J et al study that included 1479 patients conclude that troponin elevation without AMI has been seen in 87 patients.

Influence of different cut-offs on the performance of the high sensitive troponin T assay

According to one of selected study which is done by the Body et al the performance of the high sensitive troponin T assay affected to different cut offs. The findings of this study are summarized in table 5.

Table 5: Effect of different cut offs on the performance of high sensitive troponin T assay.

	At presentation		After 3 hours		After 6 hours	
	3 ng/I	14 ng/I	3 ng/I	14 ng/I	3 ng/I	14 ng/I
Sensitivity %	100	85.4	100	92.9	100	82.9
Specificity %	34	82.4	32.7	82	34.5	82.9
PPV %	47.7	60.8	19.2	45.2	29.3	56.9
NPV %	100%	92.5	100	98.6	100	94.7

PPV: Positive productive value.
NPV: Negative productive value

THE DISCUSSION

This systematic review included 3026 patients from 4 studies and it was aimed to evaluate the performance of high sensitive troponin T assay at presentation by studying its sensitivity and specificity and compare them with the conventional troponin assay. Although there are some studies claim on the performance of high sensitive troponin T assay to rule-in or rule-out myocardial infarction (Sherwood et all, 2014). The finding of this systematic review showed that this assay has better performance than conventional troponin assay at presentation and it is extremely sensitive assay can help physician to recognize the acute myocardial infarction early before other complications can develop. This systematic review showed that the mean sensitivity of hs-Tn assay at presentation is 83.5% compared to conventional troponin assay that has 65%. However, the conventional troponin assay is the better in the specificity. Its specificity is 90.7% compared to hs-Tn T assay which has 76.8%. These results indicate that the hs-Tn T assay has better sensitivity than conventional troponin assay at presentation. However, the conventional troponin assay has better specificity. This is because the hs-Tn T assay detects a very low amount of troponin that can be as result of many conditions other than myocardial infarction. According to the findings of this systematic review these conditions include apoptosis, stress, heart failures, chronic kidney renal disease, and sepsis. These results are supported by Sherwood et al, 2014 who conclude that troponin can be elevated as result of trauma, chronic kidney disease, sepsis, stress and pulmonary embolism. Thus, this assay detects level of troponin without identifying the cause (Beck, 2014) and single troponin elevation is not enough to final diagnosis of AMI. In addition to this, it indicates that the early diagnosis of AMI must not rely only on high sensitive troponin T assay because there is possibility of false positive cases. Another important finding was that some types of troponin assay has very low sensitivity that should be kept in consideration. These types include Triage and Toyo Turklab conventional troponin assay that used by Ismail Biyik et all. These two assay has 29.41% and 47.13% sensitivity at presentation. Furthermore, this assay has to be standardized and there is need to develop universal guideline to use it perfectly to avoid false positive cases.

Furthermore, the universal definition of AMI which with states that "Myocardial injury is detected when blood levels of sensitive and specific biomarkers such as cardiac troponin (cTn) are increased" (Thygesen et al., 2013) should be more accurate and it must not rely more on troponin elevation due to other health conditions that can increase the level of troponin. Thus, the physicians should be careful when they interrupt the result of hs-Tn T assay and they should not rely on the result of this assay without looking to other parameters. Another important issue that must be taken into consideration is the effect of the serial measurement of troponin on the accuracy of high sensitive troponin T assay and improving diagnosis of acute myocardial infarction. According to the finding of the Body et al who included 180 patients the sensitivity and specificity of high sensitive troponin assay increase in the second measurement than the first measurement that has been taken at presentation. This finding is supported by a study done by (Irfan et al., 2013) that showed that the accuracy of high sensitive troponin T assay increased when multiple values are taken instead of single value. In addition to this, according to Thygesen et al., 2010 the second measurement of troponin should be obtained after 6-9 h and the third one after 12-24 h. So, the laboratories

should develop new algorithms to determine if there is significant change occur when serial measurement of troponin are taken and it is very helpful to recommend that the physicians must not depend on single troponin value in diagnosing AMI rather than multiple values and the term of positive or negative troponin should be avoided because the high rise in troponin level mostly as results AMI and constant level mostly due to chronic cardiac disease (Twerenbold R et all, 2012). Thus, there is a high need to define the change in troponin pattern. Finally, According Freund et all 2011 the performance of the HsTnT assay is affected by the renal function test and this finding must be kept in consideration by the physicians while interrupting the results of this assay. This finding is supported by Scheven et all who found that HsTnT increase in chronic renal disease. Also, (Chenevier-Gobeaux et al., 2013) who conclude that performance of the hs-Tn T assay is influenced by renal function test and age. However, this area need to be searched more.

Comparison with other studies

The findings of this systematic review are supported by meta-analysis Al-Saleh et al, that evaluated 9 studies to assess the performance of the hs-Tn T assay in comparison to the conventional troponin assay. This meta-analysis evaluated 9186 patients and it found that mean sensitivity of hs-Tn assay at presentation is 94% compared to the conventional test that had 72% and its specificity was 73% compared to 95% of conventional troponin assay. The statistical difference between the sensitivity and specificity of these two assays was not significant. Also, a meta-analysis by Sethi et al who include 8628 patients found that there no significant difference in the sensitivity and specificity of hs-Tn T assay and conventional assay at presentation.

Recommendations

According to the finding of this systematic review and other related studies it is recommended that the high sensitive troponin T assay should be standardized and its result should be interpreted along with other available clinical information like ECG and clinical history. The European Society of Cardiology (ESC) AMI definition that concern more on the elevation of troponin is not enough. Moreover, the detection limit of the high sensitive troponin T assay should be corresponding to the 99th percentile limit of the reference distribution in healthy people to minimize the number of false-positive results and it should be calculated carefully. The gender and ethnicity should be kept in consideration. In addition to this, when there is an elevation of troponin with an absence of the evidence of acute myocardial infraction the physicians have the responsibility to search for other etiological factors other than acute myocardial infarction because the increased sensitivity of high sensitive troponin T assay does not mean that it can identify the cause of troponin elevation. Thus, it is important to differentiate the cardiac damage from non-cardiac related damage and acute from chronic cardiac damage. The acute process usually shows much rising change from chronic process like chronic renal failure and chronic heart failure (Wu et al., 2018). Moreover, the physicians should be careful when they collect samples for hs-Tn T assay because a new study showed that hemolysis can lower troponin value (Wu et al., 2018). Also, this study showed that hs-Tn T assay result should be reported within 60 minutes. Finally, according to the results of this systematic review it has been shown that defining the change pattern of troponin level could be helpful to differentiate the AMI from Non-AM (Twerenbold R et al, 2012). Thus, the medical laboratories should develop new algorithms to determine if there is significant change occur when serial measurement of troponin are taken and to see if this change has a significant affect to the final diagnosis of myocardial infarction and this change pattern should be defined to improve the diagnose of AMI.

Limitation

This systematic review has several limitations. First of all, the comparison between the high sensitive troponin assays and conventional troponin assays was affected by different cut-offs points that have been used by the studies that made the comparison more difficult. Also, the different types of conventional troponin assays that has been used to study performance of conventional troponin assay do not allow accurate comparison. Finally, English language studies were only included so maybe other language relevant studies are ignored.

CONCLUSION

In the conclusion, this systematic review showed that both conventional troponin assay and high sensitive troponin T assay has good accuracy. However, the hs-Tn T assay has better sensitivity at presentation and can improve the early diagnosis of myocardial infarction if its result will be interrupted carefully.

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