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Title: A Comparative study on incidence of New Onset Arrhythmia among Critically ill Medical patients in relation to Troponin levels

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Cardiac arrhythmia is a well known complication in critically ill patients and is a major cause of morbidity and mortality among them. Arrhythmias result from abnormalities of electrical impulse generation, conduction or both.Critically ill patients can have metabolic, acid - base and hemodynamic abnormalities which can many time leads to a state of vulnerablity of myocardium and triggers that are needed for arrhythmogenesis. Critically ill patients are predisposed to new onset arrhythmia because of their baseline co morbidities, acute ischemic and neurohormonal stressors and other pathophysiological changes of acute illness leading to myocardial damage. Cardiac troponin is a biomarker of myocardial damage. Elevation in troponin levels appears to be correlated with several inflammatory and endothelial factors. Abnormal myocardial microcirculation, endothelial dysfunction, abnormality of beta receptors, circulating or local factors produced by bacteria, the inflammatory response cells, catecholamine toxicity from vasopressors used in treatment, endothelial overproduction of nitrous oxide, TNFalpha, and interleukins, abnormal hemodynamics all could induce reversible myocardial injury and results in the passage of troponin fragments through membrane gaps of myocardiocytes(1). As a consequence of myocardial injury as evidenced by elevated troponin, but not caused by plaque rupture in a particular vessel and territory, this is termed as type II Myocardial infarction (2). High serum levels of troponins predict increased severity of sepsis and higher mortality(3). TNF alpha & IL1 beta are the most important cytokines of sepsis. They have a negative ionotropic effect on cardiomyocyte contractility. Along with interleukins 6, 8 and 10, these cytokines causes, leakage of calcium ions from sarcoplasmic reticulum, thereby depressing the contractility and also leads to arrhythmia(4).

I. MATERIAL AND METHODS

This study is performed among critically ill medical patients admitted in medical intensive care unit of Amala Institute of Medical Sciences over a 12 month period. All critically ill patients who get admitted in medical intensive care unit for non cardiological illness, with MEWS ≥5 were enrolled in the study.

Exclusion criteria

Those presenting with any arrhythmia at the time of admission to Medical ICU,having a pacemaker,undergone a recent cardiac interventionandwith MEWS Score below 5.

STUDY SAMPLE

Critically ill patients admitted in medical ICU for non- cardiac illness with MEWS ≥5 were enrolled in the study. They were categorized into two groups those with high troponin levels ≥ 0.1 µg/L and those with low troponin level <0.1 µg/L. They were followed up during entire ICU stay. Sample size was 230.

STUDY TOOL

- 12 LEAD ECG
- High sensitive troponin I: VIDAS High sensitive troponin I is an automated quantitative test based on one step enzyme immunoassay sandwich method with a final fluorescent detection.(ENZYME LINKED FLUROSCENT ASSAY). Consecutive sampling technique was used.

II. STATISTICAL ANALYSIS

The data will be entered in to excel work sheet and the analysis is performed using SPSS23 licensed to Amala Institute of Medical Sciences. Results on continuous measurements are presented on Mean±SD, and results on categorical measurements are presented in number (%). Significance is assessed at 5%level. Normality of data will be tested. If the difference of continuous measurements is normal, the arrhythmia positive and negative groups are analysed by independent sample't 'test. If not normal, the difference of measurements, in arrhythmia positive and negative groups are analysed by Mann Whitney test. The

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association between co-morbidities, ICU interventions and arrhythmia status are analysed by Chi square test, Fisher's exact test and odds ratio.

III. OBSERVATIONS AND RESULTS

This study evaluated a total of **260** critically ill patients admitted in intensive care unit who fulfilled the inclusion criteria. At the time of admission to ICU, serum troponin of the critically ill patients has been sent and based on that they have been divided into two groups and followed up during their ICU stay.

Of the total 260, two groups were obtained,

- Troponin I levels ≥0.1 (positive)- 130 patients and
- Troponin I levels <0.1 (negative) - 130 patients.

These two groups were followed up for the development of new onset of arrhythmia until they have been shifted out of ICU.

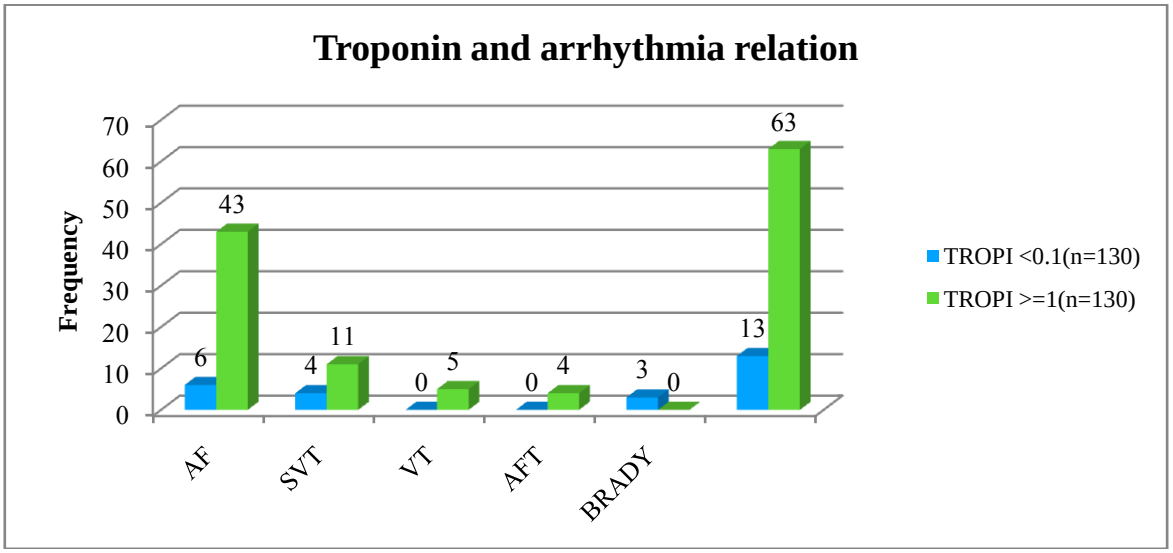
Table 1: Showing relation between Troponinelevation and Arrhythmia

Troponin and arrhythmia relation						
	TROPI <**0.1**(n=130)		TROPI ≥**0.1**(n=130)		Total	P value
	Frequency	Percentage	Frequency	Percentage		
AF	**6**	**4.6**	**43**	**33.07**	**49**	**0.0001**
SVT	4	3.07	11	8.4	15	0.063
VT	0	0	5	3.8	5	0.008#
AFT	0	0	4	3.07	4	0.018#
BRADY	3	2.3	0	0	3	0.041#
Arrhythmia	**13**	10	**63**	48.4	**76**	**0.0001**

Fisher's exact test

Out of total 260 critically ill patients 76 patients had arrhythmia during their ICU stay at hospital. So the total incidence of new onset arrhythmia in critically ill Patients was 29.2 %. Of the 76 patients who had arrhythmia, 63 (82.8%) were trop I positive and 13(17.1%) were in the trop I negative group. (T able 1.)

Among the different types of arrhythmia, Atrial fibrillation was the most common arrhythmia in ICU with a frequency of 49 (64.4%) of the total 76 arrhythmia patients. The incidence of other types of arrhythmia are SVT 15(19.7%), VT 5 (6.5%), Atrial flutter 4 (5.2%), bradyarrhythmia 3 (3.9%).



Graph 1. Showing relation between troponin and arrhythmia

Table 2: showing the mean troponin I levels in arrhythmia positive and negative groups.

	Arrhythmia		P value (Independent Samples Test)
	Yes (mean±SD) (n=76)	No (mean±SD) (n=184)	
TROPI	2.081895±3.1176244	.514571±.9547043	**0.0001**#

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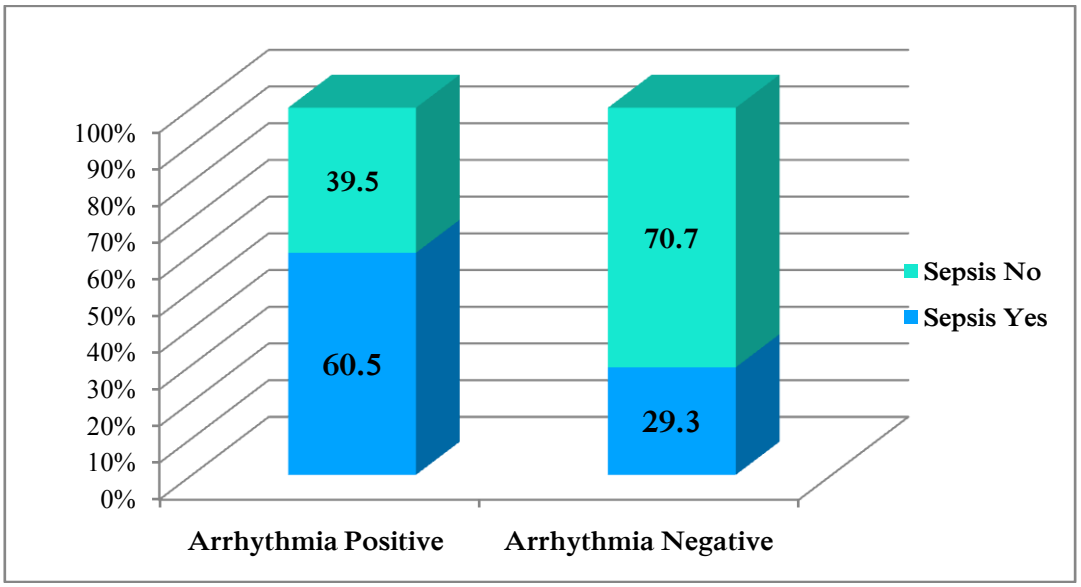
Mann-Whitney U test

Those who had arrhythmia in the study had a mean trop I value of 2.08±3.11 when compared to those who had no arrhythmia with a mean value 0.51±0.95. This had a significant p value of **0.0001** also. Thus there is a significant relation between trop I values and the incidence of arrhythmia. (Table 2)

Table 3: showing the relation between arrhythmia and sepsis

SEPSIS & ARRHYTHMIA							
	Arrhythmia positive(n=76)		Arrhythmia negative (n=184)		Total	P value(Chi square test)	Odds ratio
	Frequency	Percentage	Frequency	Percentage			
Sepsis	46	**60.53**	54	29.35	100	**0.0001**	**3.691**



Graph2. Showing the relation between sepsis & arrhythmia

It was found that arrhythmia was more common among patients with sepsis, with a frequency of **60.53%.** Among the 76 patients who had arrhythmia in the ICU, 46 had sepsis as diagnosis at the time of ICU stay. And the risk of new onset arrhythmia is about **3.6** times in the presence of sepsis. So sepsis is a major risk factor for new onset arrhythmia in ICU. (Table 3, Graph 2)

Table 4 .showing relation of arrhythmia and comorbidities

Arrhythmia & Comorbidities							
	Arrhythmia positive(n=76)		Arrhythmia negative (n=184)		Total	P value(Chi square test)	Odds ratio
	Frequency	Percentage	Frequency	Percentage			
DM	51	**67.11**	97	52.72	**148**	0.033	**1.830**
HTN	46	60.53	**116**	**63.04**	**162**	0.703	0.899

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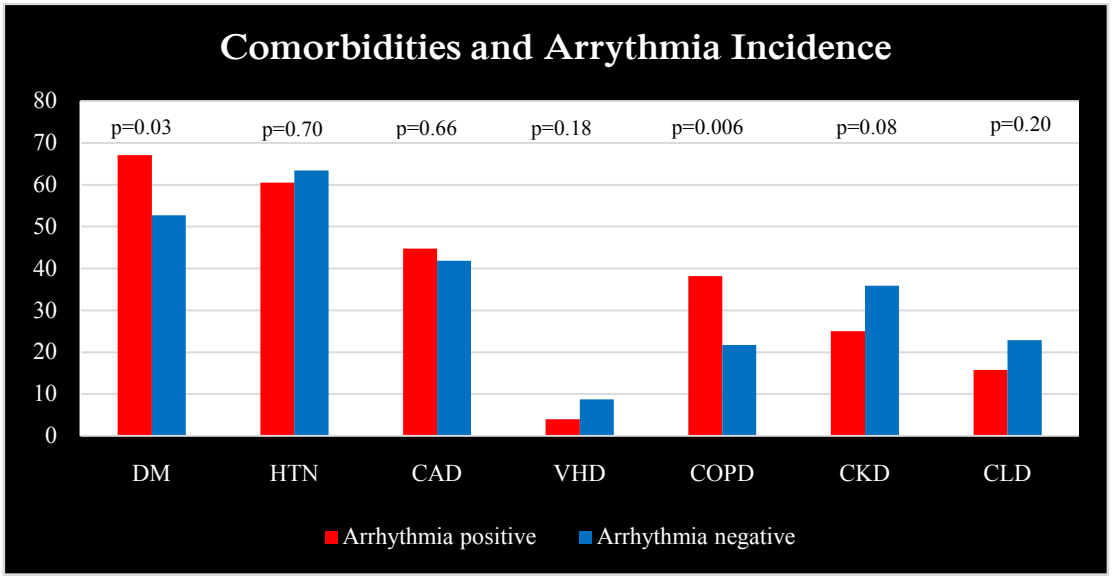
CAD	34	**44.74**	77	**41.85**	**111**	0.668	**1.125**
Structural heart d/s	3	3.95	16	8.70	19	0.181	0.432
COPD	29	**38.16**	40	21.74	69	0.006	**2.221**
CKD	19	25.00	66	35.87	85	0.089	0.596
CLD	12	15.79	42	22.83	54	0.203	0.634

In our study,we have looked for the presence of seven pre existing comorbidities like diabetes mellitus, hypertension, coronary artery disease, structural or valvular heart disease, chronic obstructive pulmonary disease, chronic kidney disease, chronic liver disease in our critically ill patients admitted in intensive care unit.

From the various comorbidities, diabetes, & chronic obstructive pulmonary disease are having the highest risk of arrhythmia. Because in the presence of diabetes, the risk is **1.83** timesand COPD the risk is **2.221** times, from the above data. And in the presence of coronary artery disease the risk is only 1.125 times for new onset arrhythmia.



Graph 3 Showing incidence of arrythmia and co morbidities among critically ill patients

We found that diabetes and chronic pulmonary disease are the common co morbidities among arrhythmia positive population. The incidence of arrhythmia in the background of pre existing coronary artery disease is almost similar in both population.(Graph 3)

Table 5: showing the relation between MEWS & arrhythmia.

	Arrhythmia		P value (Independent Samples Test)
	Yes(mean±SD) (n=76)	No(mean±SD) (n=184)	
MEWS	**7.724±1.8007**	6.696±1.6905	**0.0001**

Mann-Whitney U test

The modified early warning score is an early indicator of severity of critical illness. In this study, critically ill patient with a MEWS of ≥5 has been included. We found that as the severity of critical illness increases, the arrhythmia risk also increases. The mean MEWS score of arrhythmia

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positive population was higher **7.724±1.8007.** **(**Table 5**)**

Table 6: showing the relation between electrolytes & arrhythmia.

Electrolytes vs arrhythmia			
	Arrhythmia		P value (Independent Samples Test)
	Yes (mean±SD) (n=76)	No (mean±SD) (n=184)	
Sodium	135.566±14.7877	135.761±12.6010	0.914
Potassium	4.087±1.3723	4.541±1.2738	0.011
Magnesium	1.639±.5322	1.453±.4467	0.004
FREE CA	8.318±0.7907	8.295±1.1877	0.875

Mann-Whitney U test

The serum levels of electrolytes like sodium, potassium magnesium and calcium levels were compared between the two population groups, to assess the risk levels. Serum potassium and Magnesium values were correlative with arrhythmia while serum sodium and calcium had less impact on arrhythmia incidence.(Table 6).

Table 7 showing the relation between arrhythmia and arterial blood gas analysis.

Arterial blood gas & Arrhythmia			
	Arrhythmia		P value (Independent Samples Test)
	Yes (mean±SD) (n=76)	No (mean±SD) (n=184)	
PH	**6.9204±.39068**	**7.1793±.27084**	**0.0001**
HCO3	18.316±9.3919	17.971±6.7019	0.529#
PCO2	53.954±19.1880	47.353±12.6978	0.001
LACTATE	**3.678±2.1501**	**2.105±1.6639**	**0.0001#**

Mann-Whitney U test

Arterial blood gas analysis in critically ill patients found that lower the pH, higher the risk of arrhythmia, as the mean range of pH is **6.9204±0.39068** in the arrhythmia positive population with a significant p value. Similarly, higher lactate values which also contribute to the lower pH, are also found to be a significant risk factor of arrhythmia. Higher the lactate levels, higher the risk of arrhythmia with a mean range of lactate levels in arrhythmia positive population is **3.678±2.1501** with a significant p value.

IV. DISCUSSION

Our study conducted in 260 critically ill patients with MEWS score ≥ 5, found that the incidence of cardiac arrhythmia in this crtically ill patients was 29.2%(76/260 patients). According to the study conducted by Tongyoo et al the incidence of new onset arrhythmia in critically ill patients was 39.7% (5) and the study by Reinelt et al was 20.4%. (2). Among the various types of arrhythmia in our patients ,the incidence of Atrial fibrillation was 49 (37.6%) Atrial flutter 4 (3%), Supraventricular tachycardia 15 (11.4%), Ventricular arrhythmia 5(3.8%) and Bradyarrhythmia 3 (2.3%) respectively. The studies by Arora et al (6), koyfmann et al (7), Baumfeld et al (8)and Makrygiannis et al(9),also found that the most common arrhythmia among ICU population was atrial fibrillation.

Among the 260 critically ill patients, 130 patients had high level of Troponin during their ICU stay. The incidence of arrhythmia in these patients with those with and without high troponin values was 68.4% vs 10 % (63 patients and 13 patients respectively). The mean value of trop I levels in patients with arrhythmia was 2.08±3.11 and in patients with out arrhythmia was 0.51±0.95 ng/mL . Thus in our study we found out a positive correlation between higher troponin I levels and the incidence of arrhythmia. Thus elevations in trop I levels can be considered as a risk factor for new onset arrhythmia in critically ill patients.

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AGE

It has been found that those within the age group **61-70** form the largest subset among the cohort, of which **30.23%** are arrhythmia positive. However the group with the highest risk of arrhythmia was **71 to 80** with a percentage risk of **53.8%.**Electrical and structural remodelling associated with advancing age might provides an arrhythmogenic substrate. Also the prevalence of other concomitant risk factors of arrhythmia like diabetes, hypertension, CAD also increases among elderly. (10)

SEX

Among the 260 critically ill patients, **157** were males and **103** were females. Though females were less in number, **31%** of them had arrhythmia whereas only **28%** of males had arrhythmia. This is probably due to electrophysiological differences in females, like shorter sinus nodal recovery time, higher intrinsic heart rate and a longer corrected QT interval. Also, the influence of hormonal factors and increased life expectancy compared to males, might have contributed to this increased incidence of arrhythmia. (11).

COMORBIDITIES

Among the 148 who had diabetes, 51 (34.45 %) had arrhythmia during the ICU stay. Of the 76 who had arrhythmia in this study **51 (67.10%)** were diabetic. The incidence of arrhythmia is **1.8** times greater in the presence of diabetes.

In Framingham heart study, DM is established as an independent risk factor for AF, and recent meta- analyses published by Huxley et al revealed that patients with diabetes mellitus, had a 40% greater risk of developing AF compared to patients without diabetes. Diabetes provides an arrhythmogenic substrate such as heterogeneities in atrial and ventricular repolarization, the extent of myocardial damage, scar formation, autonomic system distortion, glucose fluctuations as well as structural and electrical alterations.(12).

History of hypertension was present in 162 patients, of which 46 had arrhythmia. Of the 76 who had arrhythmia in our study, **46 (60.53%)** were hypertensives.Hypertension results in ventricular hypertrophy which is characterized by increased myocardial mass, proliferation of fibrous tissue and decreased intracellular coupling, which lead on to in homogeneity of electrical properties and propensity to various arrhythmias. (13).

In this study, total 111patients had the co morbidity of ischemic heart disease. In the, troponin I positive, population of 130 patients only 60 (46.15%) had the co morbidity of prior ischemic heart disease. Though the study had 111 patients with prior history of ischemic heart disease only 60 of them were in the troponin I positive population. So troponin I elevation is a better predictor for new onset arrhythmia than the presence of the ischemic heart disease. Also it indicates that other than the coronary artery disease there are multiple factors that contributes to troponin I elevation among critically ill patients.

The risk of onset of arrhythmia in the presence of chronic obstructive airway disease was 2.2 times. Out of the 69 COPD patients, 29 had arrhythmia. Among the different types of arrhythmia, supraventricular tachyarrhythmia was common in COPD patients. Arrhythmia in COPD may be a consequence of hypoxemia, hypercapnia, acid base disturbances that increases the heterogeneity within the ventricular wall or it could be the result of autonomic neuropathy. (14)

SEPSIS & ARRHYTHMIA

The association between Sepsis and arrhythmia is very well established in our study. Among the 260 critically ill patients in our cohort, 100 had the diagnosis of sepsis. So sepsis is the most important morbidity in critically ill patients in intensive care unit. Among the 76 critical patients who developed arrhythmia 46 had sepsis (60.5%) with an odds ratio of 3.69. Or in other words, the development of arrhythmia is 3.69 times greater in the presence of arrhythmia.

Sepsis is an arrhythmogenic substrate. In sepsis, cardiac dysfunction and arrhythmia is common due to oxidative stress, alterations of micro and macro circulations, metabolic changes, autonomic dysfunction, mitochondrial dysfunction and apoptosis. The excess release of inflammatory cytokines and nitric oxide in sepsis, also triggers the new onset arrhythmia.(15).

MEWS is a severity of illness assessment scoring system. Those who had arrhythmia had a mean MEWS score, (7.7±1.8), which indicates as the severity of critical illness increases, the risk of development of arrhythmia increases. Among the different variables in MEWS, those who had hypotension, tachycardia and tachypnoea had the higher risk of development of arrhythmia.

V. CONCLUSION

Nearly one third of critically ill patients (29.2%) with MEWS score ≥ 5 develop arrhythmia during ICU stay. Increasing age ,diabetes, chronic pulmonary disease were found to have increase the incidence of arrhythmia among critically ill

patients. High levels of Troponin is an independent predictor for arrhythmia. This biomarker may be tested in the development of new prognostic scoring systems in critically ill patients to improve their sensitivity.

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