Research Article

Early predictors of diphtheric cardiomyopathy in children leading to better survival: Is there any solution?

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ABSTRACT

Background and Objective: Diphtheria remains a fatal disease in the current era of wide spread immunization and an important cause of pediatric mortality in developing countries. Acute mortality is due to toxin-mediated diphtheritic cardiomyopathy in majority. We aimed to examine clinical spectrum of diphtheric cardiomyopathy and diagnostic tools (serum markers, ECG, Echocardiography) to assess particular findings that might predict the development of diphtheritic cardiomyopathy and poor survival.

Material and Method: For this cohort study, 67 patients having diphtheria presenting for the first time in a 3 year period were enrolled after obtaining informed verbal consent from the guardian of each child. Demographical profile, vaccination status, clinical spectrum, ECG interpretation and echocardiographic findings were recorded.

Results: Among the 67 enrolled children (M: F 2.4:1) with age ranging from 24 to 172 months (median 106 months), 56.7% subjects presented with diphtheria were non-vaccinated. Almost 37.3% had a cardiac involvement in the form of diphtheria cardiomyopathy or arrhythmia. Total 7.5% patient expired on follow up. Septal paradoxes had 76% sensitivity and 100% specificity with a positive predictive value (PPV) of 100%. Nasopharyngeal membrane had a PPV of 40.4% (P=0.42). Neck swelling had a PPV of 57.9% (P=0.02). Moderate severity score of diphtheria disease had a PPV of 90% and severe disease had a PPV of 100%. Tracheostomy at presentation having a PPV of 100% (p=0.001). Presence of arrhythmia was associated with the highest mortality (Odd Ratio 18.1; 95% CI 2.7-73.9; P = 0.0001). Presence of septal paradoxes on echo had association with the cardiac involvement (OR 10.1: 95% CI 1.2-84.6; P = 0.0005)

Conclusion: Early prediction by alone or in combination of ECG and echocardiographic marker leads to early pick up of the disease and can decrease the burden of the disease in the community. Increased immunization coverage including booster dose of diphtheria and Tetanus (DT), easy availability of anti-diphtheritic serum (ADS), early prediction and recognition and effective treatment all may reduce the incidence and mortality.

Keywords: Diphtheria, cardiomyopathy, Children, Predictors

INTRODUCTION

Diphtheria remains an important cause of pediatric mortality in developing countries. The mortality rate is still ~10% and has changed little over the past 20 years with particular reference to developed world [1]. A resurgence of diphtheria has been observed in developing nations, are largely attributed to waning vaccine immunity and social taboos leading to poor immunization coverage in children especially above 5 years of age. Acute mortality is due to toxin-mediated diphtheritic cardiomyopathy, suffocation by the pseudomembrane, disseminated intravascular coagulation, and renal failure [2,3]. The incidence of diphtheritic cardiomyopathy following diphtheria is 10%–20%, and some Indian studies reported the occurrence of myocarditis is 16-66% and the associated mortality is ~50%. Myocarditis in diphtheria is reported to be the sole independent predictor of death with an adjusted Odds ratio 25, (95% confidence interval (CI) 3.4-210.3)[4]. Clinical signs of diphtheritic cardiomyopathy become apparent by the end of 2nd week of infection but, in severe cases, may be a presenting feature [5]. Severe conduction abnormalities including tachy or brady-arrhythmias or complete heart block are reported in 50% of

patients presented with diphtheria cardiomyopathy and reported to be uniformly fatal for children[6,7]. Most of the large series describing the clinical and electrocardiographic features of diphtheria were reported in old studies, before the availability of modern electrocardiographic, echocardiographic and bio chemical measurements [8]. These studies found that the development of severe conduction defects on the 12-lead electrocardiograph were associated with a poor prognosis [9]. We have recently observed on the prognostic and predictor utility of combined echocardiographic and electrocardiography and have shown that, in some cases of diphtheritic cardiomyopathy, intervention with temporary cardiac pacemaker or off label use of IV methylprednisolone may improve the outcome. The ability to predict from simple and readily available measures whether myocarditis will develop would aid in triage and clinical management.

We aimed to examine clinical spectrum of diphtheric cardiomyopathy and diagnostic tools (serum markers, ECG, Echocardiography) to assess particular findings that might predict the development of diphtheritic cardiomyopathy and poor survival. Identification of such factors would help in planning focused screening of such patients so that they can be picked early and may be fatal outcome can be changed. This will not only decrease chances of life threatening complications but also minimize cost used to treat them. It will also help us to decrease psychosocial trauma to family.

MATERIAL AND METHOD

This cohort study was conducted at the Department of Cardiology, The Children Hospital and pediatric medicine department DHQ/Allied hospital Faisalabad, Pakistan, over a period of 3years from 1st January 2018 till 31st December 2020. These are tertiary care centers in the province of Punjab with a population of over 120 million [10'11] where we get referral from other tertiary care hospitals in the region as well both for diagnostic and management point of view. Institutional Review Board of the hospital approved the study protocol. All patients presenting to the hospital for the first time and diagnosed as diphtheria were evaluated for inclusion in the study. After obtaining informed consent from patient's parents, evaluation was performed with confirmation of diagnosis through clinical and laboratory (throat swab, serial ECG's and echocardiography) The demographic profile, residence, vaccination status, clinical spectrum, ECG interpretation and echocardiographic findings were recorded on a specially designed questionnaire proforma by the author (UR,RN) from direct caregivers including mother, father or the guardian and ECG and echocardiographic interpretation by a consultant pediatric cardiologist. The diagnosis of diphtheria was made using either one or both of the criteria i-e clinically either if the patient had a febrile illness with a characteristic adherent pseudomembrane visible in the nasopharynx or if the patient presented later (after pseudomembrane clearance) with a history of recent severe sore throat and signs of cardiomyopathy or if throat culture proven for the Corynebacterium diphtheriae [8]. Diphtheric cardiomyopathy was defined either as Symptomatic diphtheritic cardiomyopathy, the patients who developed symptoms of, and examination findings consistent with, heart failure and abnormal findings on 12-lead electrocardiography (Partial or complete right bundle branch block with "M" pattern in V1 and "W" pattern in V6, ST segment elevation or depression, complete heart block)(Fig 1) or echocardiography or Asymptomatic diphtheritic cardiomyopathy, includes children with no symptoms of heart failure, but with either clinically detected rhythm disturbances or abnormal findings on 12-lead electrocardiography or LV dysfunction on echocardiography, according to contemporary standards of pediatric cardiology [12.] Diphtheria severity score system was defined as: "mild," local symptoms (involving the nasopharyngeal region) only; "moderate," patient is systemically unwell with a "toxic" facial appearance and having fever with systemic features of neck swelling; "severe," patient is bed-bound, is unable to drink, has difficulty breathing or inspiratory stridor , needs tracheostomy or has alteration in mental status[8]. Partial immunization was defined as the children who got only 1 or 2 doses of vaccine at early infancy and did not get all the doses recommended by EPI in Pakistan. Children were considered adequately immunized if they had received three or more doses of diphtheria toxoid containing vaccine by age 2 years [4].

Patients having growth of other bacteria on throat culture even suspected clinically as diphtheria were excluded from the study. Several variables were compared among the survivors and non-survivors to define the predictors of outcome. Outcome was defined as either developed cardiomyopathy or not.

STATISTICAL ANALYSIS

Data was entered in SPSS version 20 and analyzed using its statistical package. Frequency was calculated for qualitative variables including gender, vaccination status, and cardiomyopathy. Data was presented as mean, SD and median. Between groups comparison was done using Chi-square test for categorical data and Students' t-test and Mann Whitney U test for parametric and non-parametric data respectively Univarient and multivarient analysis were performed to determine significance and to identify the predictors having a significant association with cardiomyopathy and mortality. Odd's ratio with 95% CI was computed for the significant variables. All variables found to be significant on univariate analysis (P<0.05).

RESULTS

Sixty-seven subjects presented with diphtheria were recruited in the study in a 3 year period. There were 47 (70.1%) boys and 20 (29.9%) girls with boys to girl's ratio of 2.4:1. Median age at the time of presentation was 106 months (range 24-172 months). Median day of presentation to a tertiary care hospital was 3 days (range 1-9 days). Nearly 58.2% patients belong to rural areas. In total 38 (56.7%) subjects presented with diphtheria were non-vaccinated for diphtheria vaccine and 18 (26.9%) were completely vaccinated and 11(16.4%) were partially vaccinated. None of the subject in this cohort was given a booster vaccine at 5y of age. Total 70.1% patients had a nasopharyngeal membrane during initial presentation and 28.4% (n=19) had a neck swelling initially at presentation and 11.9% presented with stridor. All the patients who presented with stridor at initial clinical manifestation need a tracheostomy at subsequent days due to overt or impending upper airways obstruction. Majority (83.6%) of children presented with mild severity of the disease. Only 1.5% patients presented with severe disease and toxic look.

Table 1: Comparison between cardiomyopathy VS no cardiomyopathy

Variable	Cardiomyopathy	No Cardiomyopathy	P value
Total patients	25	42	--
Age (months, Median, range)	110(48-157)	105 (24-172)	P<0.003
Gender	M:F= 3 : 1	M:F= 2:1	NA
Un-Immunization (n, %)	13 (52%)	25(59.5)	P= 0.213
Partial immunization (n, %)	3 (12%)	8(19)	P<0.004
Adequate immunization (n, %)	9 (36%)	9 (21.5)	P<0.002
Neck swelling (n,%)	11(44%)	8(19%)	P=0.249
Tracheostomy (n, %)	8 (32%)	0	P= 0.650
ECG (RBBB) (n, %)	3 (12)	1(2.4%)	P=0.389
ECG (ST segment changes) (n, %)	6 (24)	1 (2.4%)	P=0.671
Echocardiography (LV dysfunction) (n, %)	15(60)	0	P=0.690
Septal paradoxes	19 (76%)	0	P<0.0001
Mild LV dysfunction (>45%)	13 (52%)	0	P<0.001
Time of presentation	3 (2-9)	3 (1-5)	P<0.0021
Deaths (n, %)	5 (20%)	0	P<0.038
EF <35% and death	5 (100%)	--	P<0.016

In all the affected cases 25.4% patients had a positive throat culture for the Corynebacterium diphtheriae. Both the electrocardiography (ECG) and echocardiography were different at initial presentation and subsequent follow up. Out of these 76.1% (n=51) had a normal ECG at initial presentation (65.7% at subsequent ECGs), 4 (6.0%) had a right bundle branch block (RBBB), 3% had a 1st degree heart block (10.4% on subsequent ECGs), 1.5% had complete heart block (3% on subsequent ECGs), 1.5% had VT (4.5% on subsequent ECGs). Forty-nine patients (73.1%) had a normal echocardiography at presentation, 23.9% (n=16) had septal paradoxes at initial echocardiography and 3% (n=2) had a LV systolic dysfunction (22.4% on subsequent echocardiography).

Twenty-five (37.3%) had a cardiac involvement in the form of diphtheria cardiomyopathy or arrhythmia. The mean interval between onset of respiratory symptoms and myocarditis was 5.9 ± 2.4 days (range 2-11 days). Among the cardiac involvement with LV dysfunction 52% had a mild LV dysfunction (EF>45%) on echocardiography and 18.8% had a moderate LV dysfunction (EF 35-45%). 7.5% (N=5) patient expired on

follow up. Among total 25 patients who had diphtheria cardiomyopathy 20% expired during follow up. All the patients who expired had moderate to severe LV dysfunction and expired primarily due to cardiomyopathy and two patients had an associated arrhythmia in the form of VT that ultimately lead to their death. All the patients were managed with inotropes (Milrinone infusion) and for VT antiarrhythmic drugs (Amiodarone, Lignocaine) were used but alternate tachy-bradyarrhythmia ultimately leads to the bad prognosis of these patients. The analysis among both the groups were given in **Table 1** .

Male had more commonly cardiac involvement as compared to female with a male: female 3:1 as compared to 2:1 among non-cardiomyopathy patients. Almost half (52%) were unimmunized in the group involve the heart but it is not statistically significant (p=0.213). patients who had neck swelling as initial presentation had a more cardiac involvement as compared to no neck swelling (44% vs 19%). Eight patients (32%) of patient who had a tracheostomy subsequently had cardiac involvement.

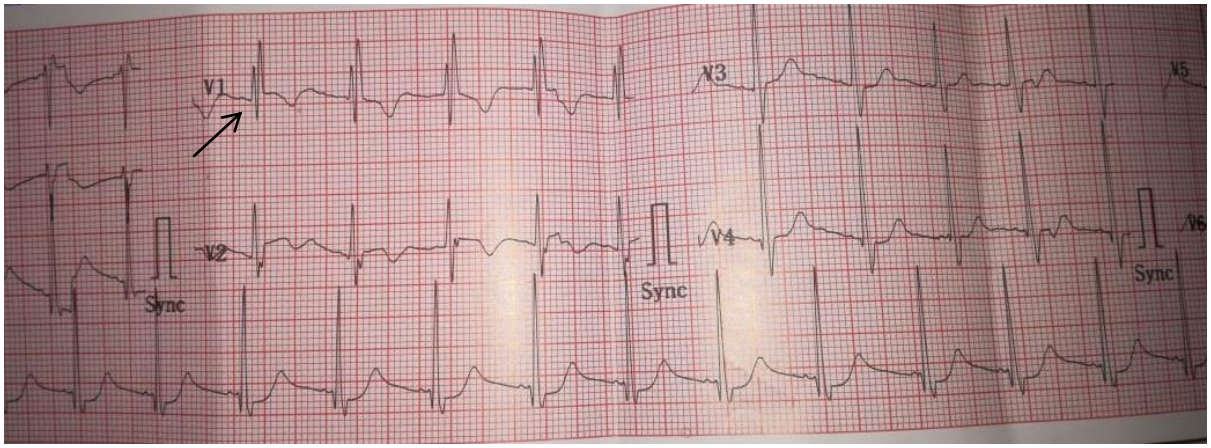
There were many predictors that predict the subsequent cardiac involvement and ultimately the outcome of the patient's. Septal paradoxes was an important marker in the prediction of the cardiomyopathy in patients with diphtheria. Septal paradoxes had 76% sensitivity and 100% specificity with a positive predictive value (PPV) of 100%. Nasopharyngeal membrane had a PPV of 40.4% (P=0.42). Neck swelling had a PPV of 57.9% (P=0.02). Moderate severity score of diphtheria disease had a PPV of 90% and severe disease had a PPV of 100%. Tracheostomy at presentation having a PPV of 100% (p=0.001). Some parameters had a very strong positive predictor value regarding outcome of the disease in the form of death. Ventricular tachycardia (VT) at presentation or on subsequent ECG had a PPV of 94% and complete heart block had a PPV of 82%.

Out of 25 patients with myocarditis 5 (20%) died (Odd's ratio 14.3, 95% CI 3.1-68.5, P = 0.0001);. Presence of arrhythmia was associated with the highest mortality (OR 18.1; 95% CI 2.7-73.9; P = 0.0001). Presence of septal paradoxes on echo had association with the cardiac involvement (OR 10.1: 95% CI 1.2-84.6; P = 0.0005) **Table 2**

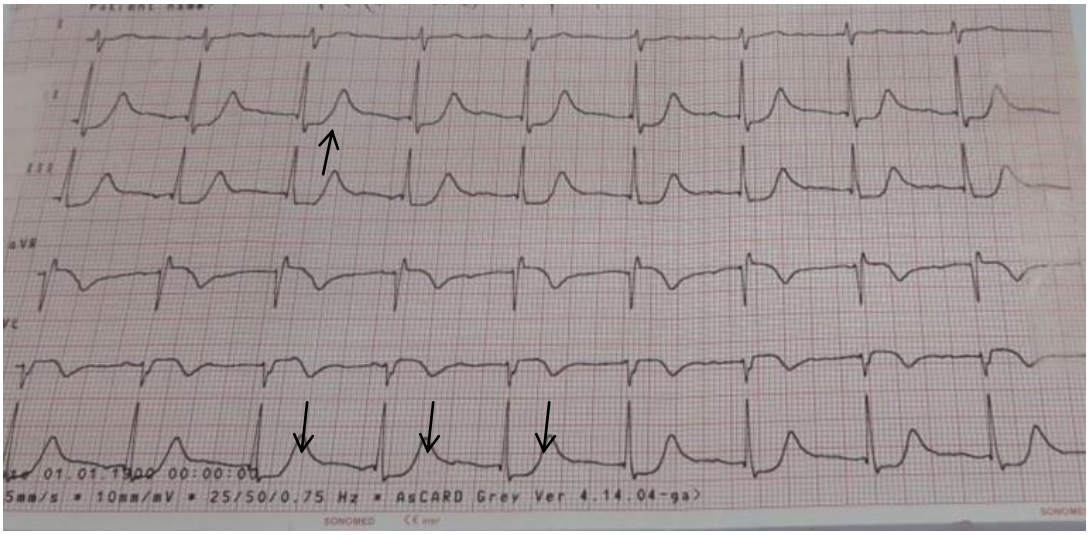
Table2: Comparison of Survivors vs Non-survivors (Complications) and risk

Complications	Survivors (n=62)	Non survivors (n=5)	Odd's Ratio (OR)	95% Confidence limit for OR	P value
Airway compromise	06	02	0.63	0.11-3.5	0.310
Neck swelling	17	02	1.7	0.31-9.2	0.480
Inspiratory stridor	07	03	4.9	1.0-25.1	0.002
Tracheostomy	07	01	1.8	0.2-14.5	0.009
Myocarditis	20	05	14.3	3.1-68.5	0.0001
Septal paradoxes	15	04	10.1	1.2-84.6	0.0001
Arrhythmia	11	05	18.1	2.7-73.9	0.0005

Fig 1= ECG changes partial RBBB (i) and ST segment changes (ii) in diphtheria cardiomyopathy

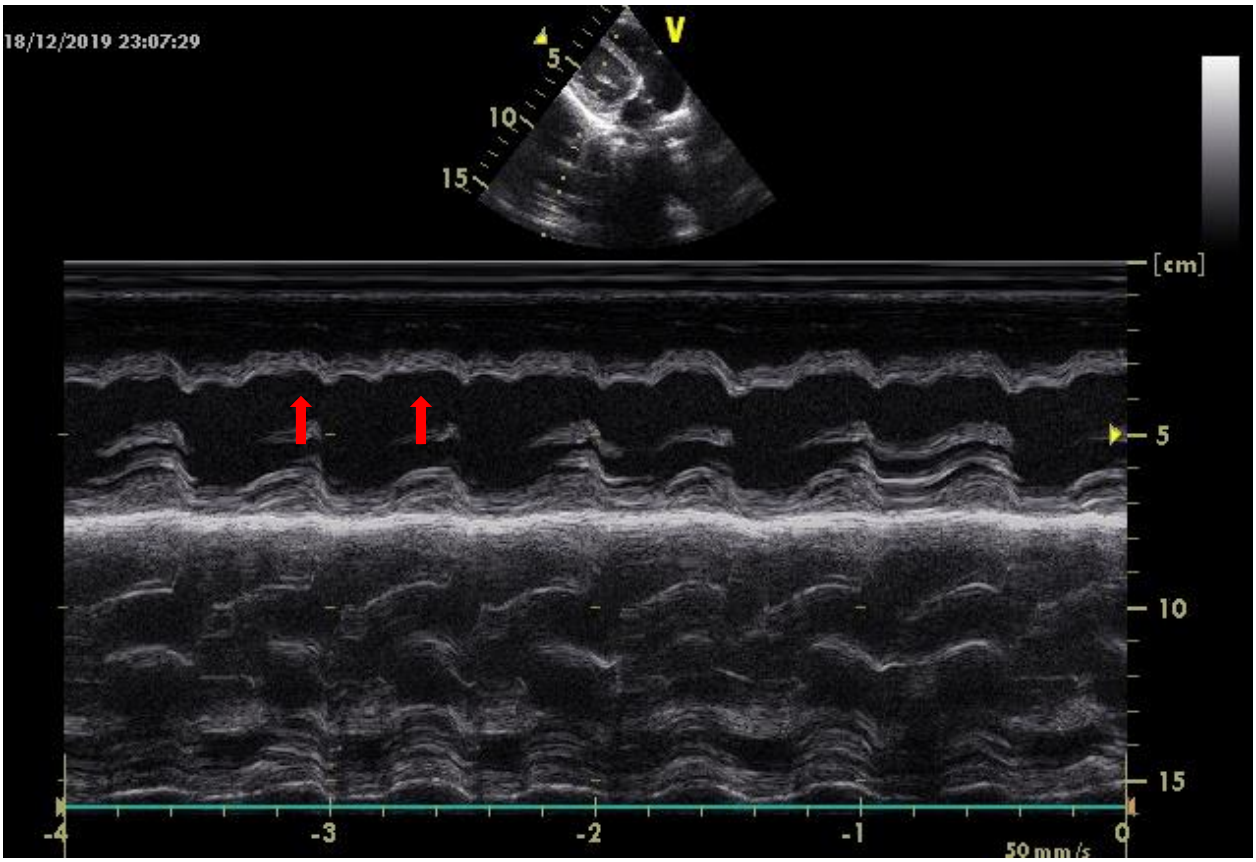


(i)



(ii)

Fig 2= Septal paradoxes in echocardiography



DISCUSSION

Diphtheria, caused by toxigenic strains of Corynebacterium diphtheriae, is an ancient disease with a significant high incidence and mortality that has always been characterized by epidemic waves of occurrence and is more common in winter in Pakistan. There are sporadic cases of diphtheria and cardiomyopathy associated with diphtheria in the developed world [13] but it is still a significant cause of mortality in developing world like Pakistan.

In this study, we demonstrated the early predictors of diphtheria cardiomyopathy aiming at early detection and pick up of the disease and prompt response may alter the outcome of the disease. There was male predominance

in our study and it is comparable with the literature [14, 15.] The Male: Female is 2.3:1 which is comparable to regional literature as well [14]. Median age at the time of presentation was comparable with other studies also had a range of presentation 62-120 months [4, 15, 16.] In this study and the related literature the cluster of diphtheria among age group of 5-10y is possibly due to lack of booster dose (DT). Patients less than 5 year are possibly rare because of immunization effect and also maternal antibodies in the younger infants. So with advancing age due to possible modifying response of antibodies due to lack of booster dose is likely reason for common presentation of diphtheria at this age group. Almost half of subjects presented with diphtheria were non-vaccinated for diphtheria vaccine and 26.9% were completely vaccinated which is comparable to the regional data[4] in which 56.3% were non immunized. Although immunized and partially immunized children were also presented with diphtheria but their number is less and likely diminished efficacy of administered vaccine at early age group is the reason of this presentation. It is possibly the reason of immunization status that the majority 58.2% children belong to rural areas of Pakistan.

The diphtheria cardiomyopathy usually associated with exotoxins mediated myocardial injury produced by these microorganisms [16.] The incidence of diphtheritic cardiomyopathy following diphtheria is 10%–20%, and some Indian studies reported the occurrence of myocarditis is 16- 66% and the associated mortality is ~50% [4, 16.] Our study showed 37.3% had a cardiac involvement in the form of diphtheria cardiomyopathy or arrhythmia. The mean interval between onset of respiratory symptoms and myocarditis was 5.9 ± 2.4 days (range 2-11 days). Majority of the patients with myocarditis were asymptomatic, had only ECG changes, SGOT elevation, and early changes in the echocardiography and had a favorable outcome. Out of 25 patients having diphtheria cardiomyopathy there was 20% expired during the course of treatment. Overall mortality among diphtheria patients was 7.4% which is comparable to the local and regional data [14,15] where it was 8.9% and 5% but the 20% expiry among diphtheria cardiomyopathy is significantly low as compare to study by Jayashree M, Shruthi N et al [4] where the frequency was above70%. This expiry rate was irrespective of the anti-diphtheritic serum (ADS) administration because almost all the patient got the ADS at admission. It was observed that almost all patients developed cardiac involvement within first week of onset of respiratory symptoms and patients who had bull neck and extensive faucial patches had more incidence of cardiac involvement and this is comparable to the literature as well [4,17.] Occurrence of diphtheria and cardiomyopathy related to diphtheria is also a seasonal trend and more common in winter particular from October to January in Pakistan and this is comparable to regional data [18], so this also depicts the seasonal trend of diphtheria cardiomyopathy.

There are many predictors of the diphtheria cardiomyopathy like nasopharyngeal membrane (PPV=40.4%), neck swelling (PPV=57.9%) immunization status (PPV=11.2%) but multivariate regression analysis found all of them non-significant as a predictor of diphtheria cardiomyopathy similar to regional data [4]. Among predictors the presence of septal paradoxes in initial echocardiography had a PPV of 100% (p=0.001) severity score had a PPV 100% (P=0.001). So by doing serial echocardiography in the early course of disease (on alternate days) we can easily predict that patient will develop the cardiac involvement or not and this is the time period where you can intervene and may change the outcome of the disease and reduce both mortality and morbidity. Serial ECGs (on daily basis) and presence of RBBB and ST segment changes initially was also a good predictor of diphtheria cardiomyopathy in combination with echocardiography findings.

On comparing the survivors with non-survivors, it was observed that later were unimmunized, more neck swelling, early tracheostomy and had more complication as compared to survivors. Development of diphtheria cardiomyopathy (OR 14.3, 95% CI 3.1-68.5, P = 0.0001), Arrhythmia (OR 18.1; 95% CI 2.7-73.9; P = 0.0001), septal paradoxes (OR 10.1: 95% CI 1.2-84.6; P = 0.0005) are the independent predictor of development of diphtheria cardiomyopathy leading to death. So by using these predictors alone or in combination and intervening early we may be able to change the fate of these children in context to mortality.

STUDY LIMITATION

There was an inherent limitation of collection of data from two or three tertiary care hospital settings in the study and it only included the patients who did reach to such facilities and may missed some patients who are sick enough and either treated locally or unable to reach the tertiary care hospitals. Also there is a need of further studies that address giving prompt management in these predicted patients so that their outcome may change towards no mortality and no morbidity.

CONCLUSION

Diphtheria is still a public health problem in many developing countries and remains the major cause of morbidity and mortality due to lack of implementation of extended program of immunization (EPI) and also the booster dose of diphtheria in our setup. Diphtheria with its worst complications like diphtheria cardiomyopathy is still highly prevalent in this region of the world and major cause of mortality among diphtheria patients. Early prediction by alone or in combination of ECG and echocardiographic marker leads to early pick up of the disease and can decrease the burden of the disease in the community Strict public health measures like an increased immunization coverage including booster dose (DT), easy availability of anti-diphtheritic serum (ADS), early prediction and recognition and effective treatment all may reduce the incidence and mortality.

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Nil

CONFLICT OF INTEREST
None

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