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Short Communication

Determinants of mortality in relationship between clinical and laboratory characteristics with the outcomes of children with diphtheria: A cross-sectional study at a national hospital of Sumatra region in 2020–2023

Shinta P. Dinanti[1,2], Oke R. Ramayani[1,2] and Ayodhia P. Pasaribu[1,2*]

[1]Department of Pediatrics, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia; [2]Department of Pediatrics, H. Adam Malik General Hospital, Medan, Indonesia

*Corresponding author: ayodhia@usu.ac.id

Abstract

In 2017, diphtheria outbreaks occurred in several provinces in Indonesia; however, the epidemiological data in the country is limited. The aim of this study was to determine the association between clinical findings and laboratory parameters associated with mortality of children with diphtheria. A retrospective cohort study was conducted at Haji Adam Malik General Hospital, Medan, Indonesia, covering diphtheria patients from January 2020 to December 2023. All patients aged 1–18 years clinically diagnosed with diphtheria were considered eligible. The associations between demographic characteristics, clinical features, immunization status, complications, and laboratory profiles with mortality were determined using Fisher's exact test, and the odds ratio (OR) with a 95% confidence interval (95%CI) was calculated. Our data indicated that the clinical characteristics of myocarditis (p=0.005) and airway obstruction (p=0.003) were associated with mortality. There was also a significant association between thrombocytopenia (p=0.020) and mortality in diphtheria patients. Patients with airway obstruction were 13 times more likely to have an increase in mortality compared to patients without airway obstruction. This study highlights that clinical and laboratory characteristics could be associated with in-hospital mortality of diphtheria cases, and therefore, pediatricians should be aware of the presence of those characteristics to prevent the mortality of the patients.

Keywords: Pediatric, infectious disease, diphtheria, *Corynebacterium diphtheriae*, pseudo-membrane

Introduction

Diphtheria is an acute infectious disease caused by Gram-positive anaerobic bacteria, *Corynebacterium diphtheriae*, which affects the upper respiratory tract in children aged one to ten years old [1,2,3]. Diphtheria potentially causes public health problems or even epidemics because it is easily transmitted from person to person through inhaled droplets and skin contact with diphtheria carriers [4,5]. Diphtheria can be prevented by vaccination, which has been routinely implemented around the world. Yet, the global coronavirus disease 2019 (COVID-19) pandemic caused disruptions in health programs, immunization services, and surveillance of diseases that can be prevented by immunization [6]. The COVID-19 pandemic, followed by a

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regional quarantine period and travel restrictions, interrupted routine vaccination programs in various countries, including Indonesia [7-9]. People refuse to visit the doctor for routine screening and vaccination due to fear of COVID-19 infection [7-9].

In 2021, WHO announced that diphtheria had 8,368 cases worldwide [10]. In Indonesia, diphtheria cases were reported in most regions with 235 cases and 25 deaths with a case fatality rate (CFR) of 11% [4]. Despite a lower incidence rate compared to 2020 (259 cases), the mortality rate was increased compared to 2020 (13 cases) with a CFR of 5.02% [4]. This phenomenon was possibly explained by the lack of diphtheria immunization or incomplete immunization, which worsened the patient's condition [4]. In North Sumatra province, the total number of cases of diphtheria in 2019 was 17 cases (0 deaths) with the highest incidence in the district of Simalungun (5 cases) and Medan (3 cases) [3].

Diphtheria has a wide range of clinical symptoms, such as asymptomatic, difficulty swallowing, low-grade fever, sore throat, pseudo-membrane formation, and a bull neck appearance. Early clinical examination and diagnosis are the cornerstone to avoid detrimental complications such as myocarditis, airway obstruction, and muscle paralysis [11,12]. Similarly, laboratory findings also vary in diphtheria infection. Thrombocytopenia is rarely found in diphtheria infections, except in severe conditions. Thrombocytopenia was also found in 31.3% of children with diphtheria treated in the intensive care room, and a thrombocyte count of less than 150×10^9 cells/L was associated with death [13]. Leukocytosis may occur but without any pathognomonic patterns. Neutrophilia, higher levels of C-reactive protein (CRP), and leukocyte rates above 25×10^9 cells/L are associated with mortality in myocarditis associated with diphtheria [13].

To this day, diphtheria studies in Indonesia are scarce. The aim of this study was to analyze the association between clinical findings such as the presence of pseudo-membranes, bull neck, fever, sore throat, myocarditis, neuritis, and airway obstruction and laboratory results such as leukocytosis, thrombopenia, and positive culture results with diphtheria mortality in children in Indonesia.

Methods

Study design and case definition

This study used a retrospective cohort design to analyze the association of clinical and laboratory findings with in-hospital mortality in children with diphtheria treated at Haji Adam Malik General Hospital, Medan, Indonesia, during the period of 2020–2023. The study retrieved data from medical records of all patients aged under 18 years old with diphtheria based on clinical findings and bacteria culture during the study period. In this study, the diagnosis of diphtheria was classified into three categories: (1) diphtheria suspect, referred to a child presenting with symptoms of pharyngitis, tonsillitis, laryngitis, tracheitis, or a combination of these, accompanied by a non-high fever and the presence of a grayish-white pseudo-membrane that is difficult to remove and bleeds easily when removed or manipulated; (2) probable diphtheria, referred to a child with suspected diphtheria plus additional symptoms such as recent contact with a diphtheria case within the past two weeks, incomplete immunization including the lack of a booster, residence in a diphtheria-endemic area, the presence of stridor or bull neck, submucosal bleeding or petechiae on the skin, toxic heart failure or acute renal failure, myocarditis, and death; and (3) laboratory-confirmed diphtheria, referred to a suspected case with positive culture results of *Corynebacterium diphtheriae* toxigenic strain or polymerase chain reaction (PCR) positive for *C. diphtheriae* which has been confirmed by Elek test [14]. Cases with incomplete data on medical records were excluded.

Data extraction and study variables

All data were directly extracted from medical records. These data included clinical findings (presence of fever, sore throat, bull neck appearance, pseudo-membrane, myocarditis, neuritis, and airway obstruction) and laboratory findings (leukocytosis, thrombocytopenia, and bacterial culture). Other information, such as diphtheria infection status (suspect, probable, and

confirmed) and history of immunization, were also extracted. The patient's outcome was in-hospital mortality.

Myocarditis was diagnosed using electrocardiogram (ECG) findings, which included prolongation of the PR interval, ST-segment changes, loss of anterior R waves, bundle branch block, complete heart block, and supraventricular and ventricular arrhythmias [15]. Neuritis (diphtheritic polyneuropathy) was diagnosed by history taking and clinical assessment and this included paralysis of the soft palate and posterior pharyngeal wall, bulbar dysfunction, and oculomotor and ciliary paralyses [16]. Airway obstruction was diagnosed by physical examination, defined as any obstruction due to pseudo-membrane on tonsils, pharynx, larynx, nares or trachea [17].

Since the bacterial culture is the gold standard for the isolation and identification of *Corynebacterium spp*, the result of culture from any samples such as nasopharyngeal cavity, throat, wounds or skin lesions were recorded. If a pseudo-membrane was present, the swabs were collected beneath the membrane as recommended [18]. Immunization history was obtained from the patient's history, categorized as complete, no booster, incomplete or no immunization [19].

Statistical analysis

The relationship between clinical and laboratory findings with mortality was assessed using Fisher's exact test, and the odds ratios (ORs) and 95% confidence interval (95%CI) were determined using a formula as previously recommended [20]. All the analyses were conducted using the software SPPS Statistic version 27.0 (IBM, New York, US).

Results

Distribution of the cases and deaths

A total of 37 children with diphtheria were included in this study between 2020 and 2023. Based on annual cases of diphtheria, the reported number of cases decreased during the COVID-19 pandemic and increased after the pandemic ended (**Figure 1**). The number of deaths was only reported in 2020 and 2023, with 3 cases each year (**Figure 1**). During the 2020–2023 period, the mortality rate was 16.2%.

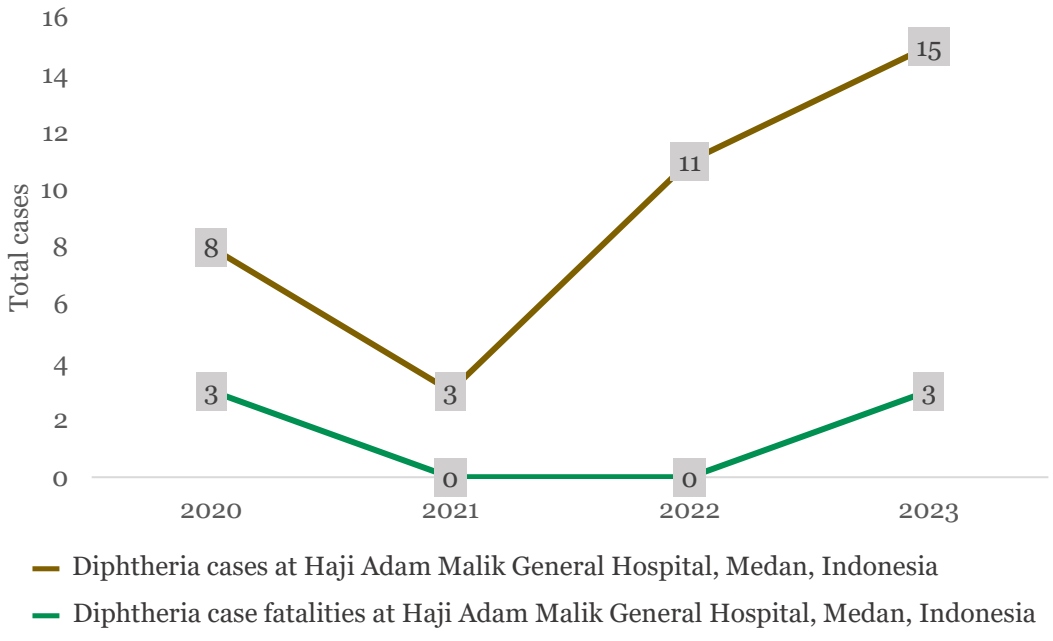

Figure 1. Diphtheria cases and deaths at Haji Adam Malik General Hospital, Medan, Indonesia, 2020–2023.

Patients' characteristics, clinical and laboratory findings

Out of the total patients, more than half of the children with diphtheria were male (56.8%), and the mean age was 8.14 years (**Table 1**). Detailed patients' characteristics and clinical and laboratory findings are presented in **Table 1**. More than half of patients did not receive any immunization for diphtheria (54.1%). All patients experienced fever and sore throat. Pseudo-membrane was found in 36 cases (97.3%), followed by bull neck appearance (73.0%) and myocarditis (45.9%). Leukocytosis was found in 78.4% of the cases while positive bacterial culture and thrombocytopenia were found in 59.5% and 51.4% of the cases, respectively (**Table 1**).

Table 1. Characteristics, clinical and laboratory findings of diphtheria cases treated at Haji Adam Malik General Hospital, Medan, Indonesia, 2020–2023 (n=37)

Variables	Frequency (%)
Sex	
Male	21 (56.8)
Female	16 (43.2)
Age, years	
Mean±SD	8.14±4.15
Median (min-max)	8 (1–18)
Immunization history	
Complete	1 (2.7)
No booster	4 (10.8)
Incomplete	12 (32.4)
No immunization	20 (54.1)
Clinical findings	
Fever	37 (100.0)
Sore throat	37 (100.0)
Bull neck	27 (73.0)
Pseudo-membrane	36 (97.3)
Neuritis	1 (2.7)
Airway obstruction	10 (27.0)
Myocarditis	17 (45.9)
Laboratory findings	
Leukocytosis	29 (78.4)
Thrombocytopenia	19 (51.4)
Positive bacterial culture	22 (59.5)
Outcome	
Recovered	31 (83.8)
Dead	6 (16.2)

Factors associated with mortality

Our data indicated no association between bull neck appearance, pseudo-membrane, or neuritis with mortality among diphtheria patients (**Table 2**). Fever and sore throat were not able to be analyzed due to data homogeneity. Leukocytosis and positive bacterial culture were also not associated with the incidence of mortality of the patients. The presence of airway obstruction, myocarditis, and thrombocytopenia were associated significantly with mortality in children with diphtheria (**Table 2**). Diphtheria patients who had airway obstruction had 13 times higher chance of mortality compared to those without obstruction (OR: 13.50; 95%CI: 1.79–101.84)

Table 2. Factors associated with mortality of diphtheria cases treated at Haji Adam Malik General Hospital, Medan, Indonesia, 2020–2023

Findings	Variables	Outcome		Odds ratio (95%CI)	*p*-value [a]
		Dead	Recovered		
		n (%)	n (%)		
Clinical findings	Fever				
	Yes	6 (100.0)	31 (100.0)	-	-
	No	0 (0.0)	0 (0.0)		
	Sore throat				
	Yes	6 (100.0)	31 (100.0)	-	-
	No	0 (0.0)	0 (0.0)		
	Bull neck				
	Yes	5 (83.3)	22 (71.0)	1.85 (0.24–13.97)	1.000
	No	1 (16.7)	9 (29.0)		
	Pseudo-membrane				

Findings	Variables	Outcome		Odds ratio (95%CI)	*p*-value [a]
		Dead	Recovered		
		n (%)	n (%)		
	Yes	6 (100.0)	30 (96.8)	-	1.000
	No	0 (0.0)	1 (3.2)		
	Neuritis				
	Yes	0 (0.0)	1 (3.2)	-	0.656
	No	6 (100.0)	30 (96.8)		
	Airway obstruction				
	Yes	5 (83.3)	5 (16.1)	13.50 (1.79–101.84)	0.003*
	No	1 (16.7)	26 (83.9)		
	Myocarditis				
	Yes	6 (100.0)	11 (35.5)	-	0.005*
	No	0 (0.0)	20 (64.5)		
Laboratory findings	Leukocytosis				
	Yes	6 (100.0)	23 (74.2)	-	0.305
	No	0 (0.0)	8 (25.8)		
	Thrombocytopenia				
	Yes	6 (100.0)	13 (41.9)	-	0.020*
	No	0 (0.0)	18 (58.1)		
	Bacterial culture				
	Positive	6 (100.0)	16 (51.6)	-	0.063
	Negative	0 (0.0)	15 (48.4)		

[a] Analyzed using Fischer's exact test
* Statistically significant at p=0.05

Discussion

Based on this study, the most common symptoms of diphtheria are fever and sore throat (100%) and bull neck appearance (73.0%). These results are comparable with a study in India in which the most common clinical findings were enlarged tonsils (99.3%), followed by fever (98.7%), sore throat (88.7%), swallowing difficulties (88.0%), and bull neck appearances (14.7%) [21]. Another study found that 100% of patients with diphtheria had a fever and severe sore throat, 93.7% had enlarged tonsils, 78.1% had bull neck appearances, and 84,8% had respiratory difficulties upon hospital admission [22]. A study found that hoarseness, dyspnea, bull neck appearance, and stridor were associated with death [23].

In the present study, leukocytosis (78.4%) was the most common laboratory finding. This is similar to another study in Indonesia that showed that leukocytosis occurred in 75.2% of cases [13]. On the contrary, a study in India with 177 cases of diphtheria showed that leukocytosis only occurred in 8.3% of cases [24]. Our data indicated that only 60% of the cases were positive for bacterial culture, similar to a previous study in India with positive culture was 65.6% of cases [25]. Studies even reported a lower rate of positive culture in diphtheria cases, less than 20% [13,26]. Although positive bacterial culture is the gold standard for *Corynebacterium spp*., several factors, such as previous antibiotic administration, inadequate sample, or transportation aspects might cause false negative results.

Our study showed that myocarditis, thrombocytopenia, and airway obstruction were associated with mortality. Published evidence showed that myocarditis is well-known to be associated with mortality in diphtheria patients [21,27,28]. Thrombocytopenia can occur in severe infections due to toxin distribution in the bloodstream. This study showed patients with airway obstruction were 13 times more likely to have an increase in mortality compared to patients without airway obstruction. Airway obstruction which could occur due to pseudo-membrane, airway edema, and bull neck, is a well-known life-threatening condition in diphtheria infection. A study in Jakarta revealed that almost 50% of airway obstruction cases in diphtheria needed further invasive airway intervention [29]. Airway obstruction was reported as the most common life-threatening complication (44%) followed by myocarditis (30%) [30]. Exotoxin is the culprit of respiratory failure, and it consists of two subunits, A and B. Subunit A has enzymatic action, which inhibits protein synthesis, while subunit B facilitates toxin binding to cellular receptors. Host response to bacteria is responsible for pseudo-membrane formation in the upper airway which is a unique finding in diphtheria infection [31].

There are some limitations of this study that need to be discussed. Although this study covered a three-year period, the sample was relatively small, so the analysis could not generate

the ORs and 95%CIs. This retrospective cohort study was unable to provide detailed information regarding the onset, contact risk, and history of traveling of the patients. In addition, not all patients with myocarditis underwent cardiac marker analysis due to resource limitations.

Conclusion

To the best of our knowledge, this is the first study to analyze the association between clinical and laboratory findings with mortality in children with diphtheria infections in North Sumatra. Our data indicated the associations between clinical (the presence of myocarditis and airway obstruction) and laboratory characteristics (thrombocytopenia) with in-hospital mortality in children with diphtheria infection. Complication of airway obstruction was associated with a 13 times greater risk of death compared to pediatric patients without airway obstruction.

Ethics approval

This research was approved by the Health Ethics Committee, Universitas Sumatera Utara, Medan, Indonesia (approval no. 1152/KEPK/USU/2023).

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Competing interests

All authors affirm that they have no conflicts of interest.

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Underlying data

Data derived to support the conclusions of this study can be obtained by contacting the corresponding author upon request.

How to cite

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