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ORIGINAL PAPER

Determining Risk Factors for Dengue Fever Severity in Jeddah City, a Case-Control Study (2017)

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Abstract

Dengue fever is a major public health problem in Saudi Arabia. Unfortunately, preventive strategies are still deficient. It can progress to severe and lethal forms, and available knowledge does not allow early prediction of which cases of dengue fever (DF) will progress to dengue hemorrhagic fever (DHF). The aim of this study was to evaluate the host and viral factors that could play a role in the progression of severe dengue cases in the frame of the revised 2009 WHO classification. Data were compiled from the Jeddah Dengue Fever Operation Room (DFOR) in the Maden Al-Fahd primary healthcare center in Jeddah. An unmatched case-control study was conducted on 123 severe cases, and 245 controls (non-severe cases) diagnosed during 2014–2016. Risk factors for severe dengue fever were secondary infection ($p = 0.02$), and co-morbidities, particularly diabetes and hypertension ($p < 0.001$). Age, gender, nationality, socioeconomic status, viral serotype, and access to health care were not significantly associated with severe disease. The main risk factors for severe dengue fever were secondary infection, and co-morbidities (hypertension and diabetes). We recommend disseminating these data to stakeholders to improve dengue control interventions in periods with anticipated high incidence.

Key words: Dengue fever, viral infection, case control, risk factors

Introduction

Dengue fever (DF) is a mosquito-borne disease transmitted by dengue virus, causing a flu-like illness that may develop into a possibly fatal complication leading to severe dengue (WHO 2017). Dengue is considered as one of the world's major public health problems. It is the most prevalent vector-borne disease that can evolve to harmful and dangerous forms and has a wide geographic spread (Paixão et al. 2015). Recent global statistics indicated that the dengue virus, which causes dengue fever, has spread widely in more than a hundred countries in the tropical and subtropical regions in the last forty years (Halstead 1988; Guzmán and Kourí 2002). It is a serious global public health problem, with 2.5 billion at risk and an annual range of 50 to 3,090 million infections, including dengue fever, dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS). Although death from dengue is said to be 99% preventable, however, it has been observed that case fatality rates (CFR) were far higher than 1% globally (Aziz et al. 2014).

Currently, dengue fever is considered a main public health problem in several parts of the Kingdom of Saudi Arabia (KSA) (Makkah, Jeddah, Jazan, and Najran) with the dramatic increase in the number of cases reported every year. The dengue virus was isolated in 1994 for the first time in Saudi Arabia at Dr. Soliman

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Fakeeh Hospital (SFH) in Jeddah from a fatal case of dengue hemorrhagic fever and a different nonfatal case (Azhar et al. 2015). Although most of the dengue infections appear as undifferentiated viral fever or end in asymptomatic infection, some of these result into fluid leakage and bleeding manifestations that cause dengue shock syndrome (DSS) and dengue hemorrhagic fever (DHF) (Azhar et al. 2015).

Dengue fever disease is diagnosed based on the existence of many symptoms, including: fever, arthralgia, myalgia, frontal headache, and a cutaneous rash, usually self-limited to one week. Asymptomatic or mild infections are often associated with primary infections. Dengue fever can be described as a severe Dengue when the patient suffers from the following symptoms: hypotension, hemorrhages, plasma leakage, and thrombocytopenia, accompanied by neurological alterations (Huy et al. 2013).

The 1997 classification of the disease by WHO differentiates DF or DHF/DSS based on symptoms like fever, hemorrhage, thrombocytopenia, and plasma leakage, which is not inclusive of all severe cases in clinical settings. Therefore, the WHO guidelines were improved in 2009 based on clinical severity (WHO 2009). Even though the WHO classification of 2009 was intended basically to be used as a clinical tool, it can also be used to divide severe dengue cases into three distinctive subcategories: severe vascular leakage, severe bleeding, and severe organ dysfunction, that permits physicians to determine the severe disease progression or pathogenesis in a specific way, which provides a more uniformed framework for clinical research (Farrar et al. 2013).

The development of severe forms of dengue fever is dependent on multiple hosts and viral factors (Martina et al. 2009). Early detection of cases progression to DHF in order to limit severity is not possible by current knowledge (Teixeira et al. 2015). Studies show that secondary infection by heterologous dengue fever virus serotypes has more potential to develop into severe disease. More severe infections can be caused by specific serotypes of the virus more than others even during primary infection with DENV-3 or secondary infection with DENV-2, DENV-3, and DENV-4 (Soo et al. 2016). A study further confirms that DENV-1 caused severe primary infections compared to other serotypes what indicates that serotypes affect severity (Anantapreecha et al. 2005).

Cumulative incidence of DHF can be less than 1% in some areas where it is considered to be endemic, which can be explained by the fact that more than 70% of the population has developed immunity to dengue fever (Teixeira et al. 2015). Other factors have to come into play for the progression to severe forms of the disease. It might be possible that the genetic makeup of the host affects the likelihood of progression to severe disease. One hypothesis suggests that chronic diseases' prior existence may influence the risk of severity (Kyle and Harris 2008).

A prospective observational study using the 1997 dengue classification for clinical purposes (Jain et al. 2017) found that co-morbidities such as diabetes mellitus, hypertension, coronary artery disease, and chronic obstructive airway disease/bronchial asthma were more common with patients with DSS. Furthermore, age > 24 years was found to be an independent risk factor for dengue fever mortality, but it was not significantly different between patients of DF and DSS. Clinical studies show that some lab measurements can be associated with severe dengue fever infection like elevated hematocrit, thrombocytopenia, and altered liver function test (Khan et al. 2013).

The government of Saudi Arabia has significantly increased the budget for mosquito control in 2006 to limit the spread of dengue fever in Jeddah; the calculated budget roughly measures up to seven billion Saudi riyals (MOH KSA 2008). Nonetheless, despite this vast expenditure, no substantial decline in dengue cases incidence happened.

The vector's and the virus's geographical spread have caused worldwide re-occurrence of the dengue disease epidemic and re-emergence of severe forms of the disease during the past 25 years (Kyle and Harris 2008). The continuous circulation of the four known dengue virus serotypes has led to a magnified frequency and magnitude of re-emerging epidemics of the disease with the increased number of cases that need hospitalization and an apparent elevation in the risk for developing severe dengue fever (Ferreira 2012). Therefore it is plausible to infer that outbreaks of a more severe form of dengue fever might be on the verge of occurring in Saudi Arabia.

This study aims to assess host and viral factors essential to the progression of the dengue fever disease into more severe forms in the light of the classification made by WHO in 2009 (WHO 2009).

Experimental

Materials and Methods

All monthly-confirmed dengue fever cases from January 2006 to December 2016 in Jeddah city were extracted from dengue surveillance database (both the old spreadsheet program and the new Health Electronic Surveillance Network (HESN) program) from the Dengue Fever Operational Room (DFOR) in the Public Health Directorate in Jeddah, Saudi Arabia. This sample was considered to include all patients to ascertain the availability of sufficient cases and controls. All dengue

cases were classified as a Severe Dengue according to the 2009 WHO classification and confirmed through the reverse transcriptase-polymerase chain reaction (RT-PCR) technique with identified virus serotype by the regional lab (Jeddah) were extracted from DFOR records. The corresponding notifying hospitals and some patients were contacted to complete missing data, and verbal consent was obtained when required.

According to the regional lab in Jeddah, viral RNA was extracted from serum samples, and RT-PCR was done by using a commercial kit, the LightMix® Modular Dengue Virus (Cat. No. 58-0700-96) (TIB MOLBIOL, Berlin, Germany) in order to detect viral RNA, and the LightMix® Reflex Dengue Typing (Cat. No. 40-0700-24), (TIB MOLBIOL, Berlin, Germany) for serotype identification. RT-PCR tests were performed on a Roche LightCycler® 480 instrument.

All dengue cases classified as non-severe dengue, according to the 2009 WHO classification, were considered controls. The data collection form was constructed in three sections. Section A for demographic and socioeconomic data and was adopted from the official notification form used by the national dengue fever control program. Section B and C for signs and symptoms data and laboratory investigations were adopted from the WHO dengue fever checklist for chart reviewers.

Data were obtained, coded, entered, and managed using the Statistical Package for Social Sciences (SPSS) version 23 and assessed for normality and multicollinearity. Proportions, charts, and graphs presented descriptive statistics of categorical variables. Mean values and standard deviations presented continuous data. Inferential statistics compared cases and controls using two independent sample t-tests for continuous variables and Chi-square test for categorical variables. Multivariable logistic regression analysis was done to variables that showed significant association with dengue fever severity to control for confounders and odds ratios.

Results

The total participants in this study were 368 patients. Severe dengue fever patients compromised 33.4% (123/368) of the sample, and 66.6% (245/368) had non-severe dengue fever. As Table I shows, there was a preponderance of males over females (male 85.1%, female 14.9%). Age distribution varied among different age groups, but most of the sample's patients were within the age group 20–29 years. Non-Saudis nationalities were predominant (73.9%), with Egyptian (18.5%) and Pakistani (15.5%) being the most frequent.

Most patients (85.1%) had no comorbidities, and (92.9%) had a primary infection with serotype 2 being the most prevalent (63%) (Fig. 1). Most of the sample's patients had outdoor jobs (42.4%); they lived in the middle of Jeddah (37%), and had seemingly equal access to healthcare services. It was measured by the number of fever days before presentation to hospital, and the mean was 3.3 ± 2.7 days.

Table I
Demographic profile of the studied sample.

	Variable	No.	%
Age by year Category	(0–9)	10	2.7
	(10–19)	32	8.7
	(20–29)	110	29.9
	(30–39)	102	27.7
	(40–49)	70	19.0
	(50-older)	44	12.0
Gender	Male	313	85.1
	Female	55	14.9
Nationality	Saudi	97	26.4
	Non-Saudi	271	73.6
Type of infection	Primary	342	92.9
	Secondary	26	7.1
Occupation	Outdoor jobs	156	42.4
	Indoor jobs	124	33.7
	Students	50	13.6
	Not working	32	8.7

Age distribution, in general, was different among cases than controls with a greater proportion of cases in the older age group ($p = 0.00$) with a mean age of 36.8 ± 32.2 years. Cases had more secondary infection ($p = 0.02$), and more comorbidities ($p = 0.00$) than controls. All other socio-demographic features tested

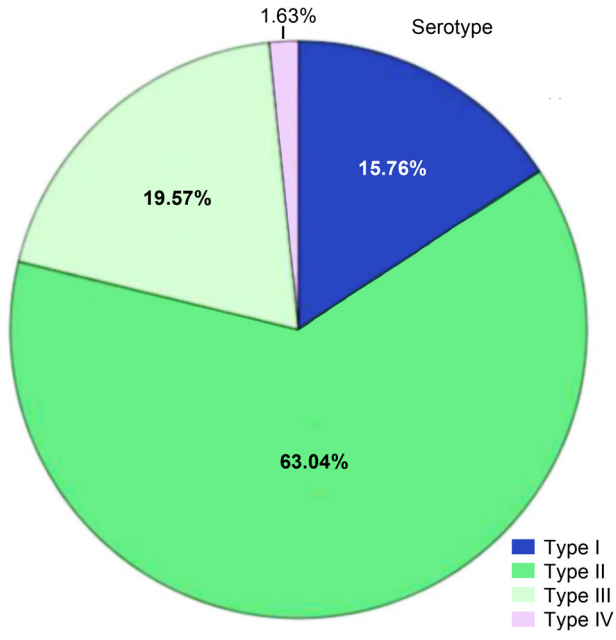

Fig. 1. Serotype distribution among the sample studied showing the dominance of serotype 2.

Table II
Comparison of severe (cases) and non-severe dengue (controls) patients' socio-demographic and clinical features.

	Characteristics	Cases No. (%)	Controls No. (%)	Significance test	*p*-value
Gender	Female	23 (41.8)	32 (58.2)	X2 = 2.048	0.12
	Male	100 (31.9)	213 (68.1)		
Age by years Category	0–9	3 (30)	7 (70)	X2 = 24.164	0.00*
	10–19	13 (40.6)	19 (59.4)		
	20–29	21 (19.1)	89 (80.9)		
	30–39	36 (35.3)	66 (64.7)		
	40–49	24 (34.3)	46 (65.7)		
	50+	26 (59.1)	18 (40.9)		
	Mean ± SD	36.8 ± 14.4	14.3 ± 11.62	T = 3.330	0.00*
Nationality	Saudi	33 (34%)	64 (66)	X2 = 0.21	0.88
	Non-Saudi	90 (33.2)	181 (66.8)		
Occupation	Outdoor jobs	53 (34)	103 (66)	X2 = 2.030	0.56
	Indoor jobs	38 (30.6)	86 (69.4)		
	Student	16 (32)	34 (68)		
	Not working	14 (43.8)	18 (56.3)		
Address	North	35 (29.4)	84 (70.6)	X2 = 2.809	0.59
	Middle	44 (32.1)	93 (67.9)		
	South	34 (39.5)	52 (60.5)		
	East	5 (35.7)	9 (64.3)		
	Outside	5 (41.7)	7 (58.3)		
Type of infection	Primary	109 (31.9)	233 (68.1)	X2 = 5.244	0.02*
	Secondary	14 (53.8)	12 (46.2)		
Access to health care (No. of fever days)	Mean ± SD	3.37 ± 3.21	3.24 ± 2.38	T = 0.528	0.598
Comorbidities	No	92 (29.2)	223 (70.8)	X2 = 20.571	0.00*
	DM	12 (70.6)	5 (29.4)		
	HTN	13 (59.1)	9 (40.9)		
	DM&HTN	2 (33.3)	4 (66.7)		
	Other	4 (50)	4 (50)		
Serotype	Type1	14 (24.1)	44 (75.9)	X2 = 5.405	0.144
	Type2	86 (37.1)	146 (62.9)		
	Type3	20 (27.8)	52 (72.2)		
	Type4	3 (50)	3 (50)		
WBC count (10^3/μl)	Mean ± SD	4.11 ± 2.87	4.22 ± 3.811	T = –0.29	0.771
Platelet count (10^3/μl)	Mean ± SD	123.8 ± 92.09	137.6 ± 99.8	T = –0.899	0.369
HTC	Mean ± SD	43.4 ± 12.9	43.5 ± 9.31	T = –0.025	0.468

The X2chi-square test was done by the SPSS software to compare categorical variables; and independent sample t-test for continuous variables with equal variance was assumed; *p* – probability value; * – statistically significant ($p < 0.05$)

in this study were insignificant between cases and controls (Table II).

A binary logistic regression was applied to verify the effects of age, type of infection, and comorbidities on the likelihood that patients will have severe dengue fever. The results showed that secondary infection [OR (95% CI) = 0.40 (0.17–0.96) $p = 0.004$] and comorbidities as a whole showed a significant prediction power of severe dengue [OR (95% CI) = 1.28 (1.06–1.55) $p = 0.009$]; however, individual separate groups of comorbidities didn't show a similar behavior. The age that was significant in the binary analysis was no longer significant after adjusting in the logistic regression analysis.

The Hosmer-Lemeshow test was chosen to test the goodness of fit for the logistic regression model since it contained more than one continuous variable. It showed a good fit of the regression model performed (Chi = 0.41, $p = 0.995$). Additionally, the classification table was made to see how successful the model is in predicting the severe dengue cases, as presented

Table III
Logistic regression analysis of predictors of dengue fever severity.

	Predictors	B	S.E.	OR (95% CI)	*p*
Age	Overall	0.22	0.10	1.24 (0.33–1.49)	0.224
	0–9	–081	0.81	0.44 (0.09–2.19)	0.319
	10–19	–0.51	0.60	0.60 (0.18–1.95)	0.394
	20–29	–1.53	–0.49	0.22 (0.08–1.57)	0.202
	30–39	–0.66	0.47	0.52 (0.20–1.30)	0.162
	40–49	–0.83	0.47	0.44 (0.17–1.09)	0.077
Type of infection	Overall	0.86	0.42	2.36 (1.03–5.39)	0.042*
	Secondary infection	–0.91	0.44	0.40 (0.17–0.96)	0.040*
Co-morbidities	Overall	0.25	0.10	1.28 (1.06–1.55)	0.009*
	D.M	–0.55	0.82	0.58 (0.11–2.90)	0.504
	HTN	0.77	1.01	2.15 (0.30–15.60)	0.449
	D.M & HTN	–0.03	0.99	0.97 (0.14–6.74)	0.976
	Others	–1.21	1.27	0.30 (0.02–3.61)	0.342

B – Logistic regression coefficient; S.E. – Standard error of logistic regression coefficient; OR – Odds Ratio; CI – Confidence Interval; *p* – probability value; * – statistically significant ($p < 0.05$).

in detail in Table III. Moreover, we have calculated the predicted value and plotted it versus observed ones, as demonstrated in Fig. 2 It showed the success of the model in predicting with most cases around the mean prediction line in close conjugation with observed ones.

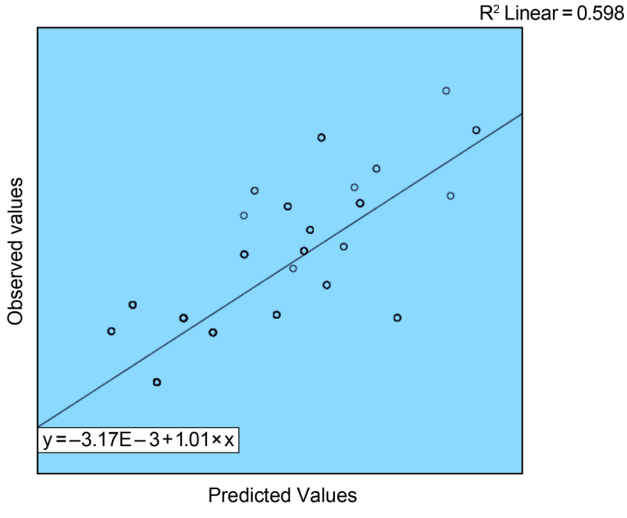

Fig. 2. Predicted versus observed values of severe dengue cases.

Discussion

Dengue fever is a major public health problem in Saudi Arabia. It is partly due to the dramatic increase in the number of cases reported every year. The aim of this study is to determine the risk factors of DF severity among cases reported between 2014 and 2016 in Jeddah. Different variables were compared between cases with severe dengue fever and controls with non-severe dengue fever. The variables studied were: age, gender, nationality, occupation, access to health care expressed as the number of fever days before hospital admission, indoor versus outdoor work, address, and serotype of the virus. Occupation and access to health care were used as an indicator of the socio-economic status of the patient.

Of significance, age, infection type, and the presence or absence of co-morbidities were the most prominent risk factors for progression to the severity of the disease. Old age subjects were more likely to develop severe dengue ($p < 0.000$) in the binary regression, but after adjusting for type of infection and co-morbidity, the adjusted odds ratio showed no significance what can be explained by the fact that subjects with old age are more likely to have secondary infections and co-morbidities. Patients who had a secondary infection and those who had co-morbidity had higher rates of severe disease progression AOR = (2.48; 95% CI: 1.04–5.99) and (3.71; 95% CI: 1.18–11.73), respectively. However, other factors did not seem to alternate the course or severity of the disease, such as gender, nationality, occupation, indoor versus outdoor work, address, virus serotype, access to health care, WBC count, platelet count, and HTC.

Following our findings, many other literature studies had reported diabetes mellitus, hypertension, and other co-morbidities as predictors for disease severity. For instance, a case-control study conducted by Pang and coworkers (Pang et al. 2012) in Singapore in 2007–2008 stated that diabetes (AOR = 1.78; 95% CI: 1.06–2.97), and diabetes with hypertension (AOR = 2.16; 95% CI: 1.18–3.96) were independently associated with dengue hemorrhagic fever.

A meta-analysis published in 2015 (Htun et al. 2015) that analyzed five case-control studies, which compared the prevalence of diabetes among patients with dengue (acute or past; controls) and patients with severe clinical manifestations. Only one study was conducted after 2009 and used the new WHO classification like ours, while other studies collected information based on the WHO 1997 classification system. The systemic review found that a diagnosis of diabetes was associated with an increased risk for a severe clinical presentation of dengue (OR 1.75; 95% CI: 1.08–2.84, $p = 0.022$), and it is a risk factor for the severity of dengue fever. On the contrary, a study from Pakistan in 2013 (Mahmood et al. 2013) did not find that diabetes mellitus, hypertension, ischemic heart disease, or bronchial asthma had an impact on increasing the risk of patients who contracted dengue fever to the risk of dengue hemorrhagic fever or dengue shock syndrome.

Unlike our study, gender seemed to be a contributing factor for predicting the severity of the disease. Female gender was significantly associated with severe dengue fever in retrospective research done by Carcasso and coworkers (Carrasco et al. 2014), aiming to explore the predictors of severe dengue fever. Unlike the results of this studied sample, the virus serotype was significantly correlated with dengue fever severity in a meta-analysis published in 2016 (Soo et al. 2016). It found that DENV-3 phenotype from the South East Asia (SEA) had a higher percentage of severe cases in primary infection, whereas DENV-2, DENV-3, and DENV-4 from the SEA region, as well as DENV-2 and DENV-3 from non-SEA regions, showed a higher percentage of severe cases in a secondary infection. Also, Guzman and coworkers (Guzman et al. 2013) reported that secondary infection was a risk factor for dengue hemorrhagic fever and dengue shock syndrome.

The information yielded by the present study will help practicing doctors to look out for predictors/risk factors developing severe forms of dengue fever in the light of data that is specific to Jeddah city, which in turn will help reduce mortality of dengue fever if severe forms were prevented.

In conclusion, the most significant risk factors for disease severity were secondary infection and the presence of co-morbidities such as diabetes and hypertension. Further studies are needed to investigate the pathogenesis of secondary infection with dengue fever and determine which serotype is more common in a secondary infection.

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Conflict of interest

The authors do not report any financial or personal connections with other persons or organizations, which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

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