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Original Article

Comparing the 2009 and 1997 World Health Organization dengue case classifications in a large cohort of South Asian patients

Umesh Jayarajah[1,2], Upul Dissanayake[3], Visula Abeysuriya[4], Pradeep K de Silva[1], Priyankara Jayawardena[1], Aruna Kulatunga[5], Harshini Fernando[5], Manohari Madarasinghe[6], Damayanthi Hapugoda[6], Lakshika Perera[2,7], Vibhavee Kannangara[2,7], Champika Udayangani[2,7], Ranga Peiris[2,7], Shuaib Faizer[7], Pamodh Yasawardene[7], Sanjay de Mel[4], Ishan de Zoysa[2,7], Suranjith L Seneviratne[2,7]

[1] Dengue Unit, National Hospital of Sri Lanka, Colombo, Sri Lanka
[2] Department of Surgery, Faculty of Medicine, University of Colombo, Sri Lanka
[3] Department of Medicine, Base Hospital, Panadura, Sri Lanka
[4] Nawaloka Hospital, Colombo, Sri Lanka
[5] Department of Medicine, National Hospital of Sri Lanka, Colombo, Sri Lanka
[6] Department of Paediatrics, Base Hospital, Panadura, Sri Lanka
[7] Dengue Research Group, Colombo, Sri Lanka

Abstract

Introduction: Due to the shortcomings in the 1997-World Health Organisation (WHO) dengue case classification (DCC), a revised classification was proposed in 2009. This study was aimed to assess the clinical usefulness of the two classifications during a large dengue epidemic.

Methodology: Clinical data of dengue patients admitted to selected units at National Hospital of Sri Lanka, Panadura Base Hospital and Nawaloka Hospital Colombo between June and August 2017 were collected prospectively. Cases were classified using the 1997 and 2009 WHO DCCs.

Results: 1,878 patients [adult = 1,573 (83.8%)] were studied. Based on 1997-WHO-DCC-DF (Dengue Fever): 1,316 (70.1%), DHF (Dengue Haemorrhagic Fever) -1: 468 (24.9%), DHF-2: 86 (4.6%) and DHF-3: 8 (0.4%). Based on 2009-WHO-DCC–Dengue with warning signs (WS): 1647 (87.7%), Dengue without WS: 231 (12.3%) and severe dengue (SD): 41 (2.18%). A total of 1,088 (82.7%) DF and 559 (99.5%) DHF patients developed WS. Of those without WS, 228 (17.3%) were DF patients and 3 (0.5%) were DHF patients. Three (0.23%) DF and 38 (6.76%) DHF patients had SD. All SD patients had WS. The level of agreement between the two systems of classification was poor (Kappa = - 0.035, $p < 0.001$).

Conclusions: The 2009-WHO-DCC was more useful than 1997-WHO-DCC in predicting dengue disease severity as few DF patients also had SD. Furthermore, the presence of WS identified patients with SD. However, the 2009-WHO-DCC may not suit the resource limited countries as WS are non-specific, and lack of diagnostic tests can result in case overload.

Key words: Dengue virus infections; 2009 WHO dengue case classification; 1997 WHO dengue case classification; Sri Lanka.

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Introduction

Dengue, a viral haemorrhagic fever is endemic in the tropics and subtropics. Frequent dengue epidemics cause a significant burden to the healthcare systems of these countries [1,2]. Recent studies, point to an increase in unusual presentations and severe disease with involvement of various organ systems [1,3-6]. The 1997 World Health Organization (WHO) dengue guidelines, classified the illness into: dengue fever (DF), dengue haemorrhagic fever (DHF), and dengue shock syndrome (DSS) [7,8]. However, due to heterogeneity in clinical manifestations, the WHO proposed a revised dengue case classification (DCC) in 2009 which classifies the disease into "dengue" and "severe dengue" [9,10]. The clinical utility of classifying patients according to the different classifications has been a matter of debate [9].

Although previous studies have compared the 1997 and 2009 WHO DCCs, the majority of the studies were conducted in Brazil and South East Asia in a retrospective sample [11-15]. Large scale prospective studies in the South Asian region is limited. Sri Lanka experienced a large dengue epidemic in 2017 [2,16]. Therefore, we evaluated the utility of the 1997 and 2009

WHO DCCs in a large cohort of Sri Lankan patients seen during this epidemic.

Methodology

This is a multicentre prospective cohort study. All inward patients with dengue admitted to two general medical wards and a specialised dengue treatment unit at the National Hospital of Sri Lanka (which is the largest tertiary care centre in Sri Lanka), a medical and paediatric ward at the Panadura Hospital (a secondary care hospital) and Nawaloka Hospital Colombo from June to August 2017 were analysed. There were no exclusion criteria. The admission criteria were based on the National guidelines for the management of dengue [17,18]. Ethical clearance for study was obtained from the Ethical Review Committees of National Hospital of Sri Lanka, Colombo (No: AAJ/ETH/COM/2017-21), Faculty of Medicine, University of Colombo and Panadura Base Hospital. Informed written consent was obtained from all participants/ guardians (in those aged less than 18 years) before including in the study. Based on the 1997 WHO DCC, the patients were classified in to dengue fever (DF) and dengue haemorrhagic fever (DHF) [19]. The clinical data were prospectively collected till recovery. The most severe level of dengue case classification was determined after convalescence. DF was defined as presence of two or more of the following symptoms in addition to fever: headache, retro-orbital pain, myalgia, arthralgia, rash, haemorrhagic manifestations, and leukopenia. DHF was defined as the presence of the following symptoms in addition to fever; a haemorrhagic tendency (at least a positive tourniquet test); thrombocytopenia (≤ 100,000 cells/mm3) and plasma leakage (based on twice daily ultrasound scan). In addition, based on the 2009 WHO DCC [9], patients were classified as having severe dengue and dengue infections (with or without warning signs). The two classification systems were compared. SPSS version 17.0 was used for statistical analysis. Parametric tests were used to determine associations. Cohen's kappa analysis was used to determine the level of agreement. A *p* value of less than 0.05 was considered statistically significant.

Results

A total of 1,878 patients [adult = 1,573 (83.8%) and children = 305 (16.2%)] were studied. A total of 1,065 patients (severe dengue = 13) were from Panadura Base Hospital (with approximately 100 health care staff and 250 beds in the medical wards), 407 patients (severe dengue = 17) from National Hospital of Sri Lanka (with approximately 300 health care staff and 1,000 beds in the medical wards), and 406 (severe dengue = 11) were from Nawaloka private hospital (with approximately 100 health care staff and 250 beds in the medical wards). A total of 145 patients had underlying diseases. Common comorbidities included diabetes -79, hypertension - 70 and dyslipidaemia - 41. Based on the 1997 WHO DCC - DF (Dengue Fever): 1316 (70.1%), DHF (Dengue Haemorrhagic Fever) - 1: 468 (24.9%), DHF-2: 86 (4.6%) and DHF-3:8 (0.4%). Based on the 2009 WHO DCC – Dengue with warning signs: 1647 (87.7%), Dengue without warning signs: 231 (12.3%) and severe dengue: 42 (2.18%). A total of 1,088 (82.7%) DF and 559 (99.5%) DHF patients developed warning signs. Of those without warning signs 228 (17.3%) were DF patients and 3 (0.5%) were DHF patients (Table 1). Three (0.23%) DF and 38 (6.76%) DHF patients had severe dengue. All severe dengue patients had warning signs. In adults, the percentage of severe dengue was < 0.3% in DF and DHF1, 33.7% in DHF 2 and 100% in DHF 3, whereas in children 0% in DF and DHF1, 29% in DHF2 and 100% in DHF3. Of those classified as having severe dengue (N = 42), five had severe plasma leakage, 29 had severe bleeding, 3 had signs of severe organ impairment and one had both severe bleeding and organ impairment.

Table 1. WHO classification 1997 vs. 2009.

				Dengue				Severe Dengue			
		Total	%	Without Warning Signs		With Warning Signs		Yes		No	
				N	%	N	%	N	%	N	%
DF/DHF	DF	1,316	70.07	228	17.33	1,088	82.67	3	0.23	1,313	99.77
	DHF1	468	24.92	3	0.64	465	99.36	1	0.21	467	99.79
	DHF2	86	4.58	0	0.00	86	100.00	29	33.72	57	66.28
	DHF3	8	0.43	0	0.00	8	100.00	8	100	0	0
DF/DHF	DF	1,316	70.07	228	17.33	1,088	82.67	3	0.23	1,313	99.77
Overall	DHF	562	29.93	3	0.53	559	99.47	38	6.76	524	93.24

Table 2. Clinical characteristics of the patients classified according to the 1997 and 2009 WHO dengue case definitions.

		1997 Classification [a]				Dengue with warning signs [b]				Severe dengue [c]			
		DF (N = 1,316)		DHF (N = 562)		Yes (N = 1,647)		No (N = 231)		Yes (N = 41)		No (N = 1,837)	
		N	%	N	%	N	%	N	%	N	%	N	%
Gender	Male	813	61.78	361	64.23	1,039	63.08	140	60.59	30	73.18	1,144	62.31
	Female	503	38.22	201	35.77	608	36.92	91	39.41	11	26.82	693	37.69
Age (Mean/SD)		32.54	15.87	33.12	14.48	32.23	14.19	30.39	16.10	32.00	13.21	31.77	14.58
Headache		891	67.71	405	72.06	191	12.48	133	56.36	32	76.19	1,089	59.31
Myalgia		447	33.97	190	33.81	181	11.80	59	25.0	17	40.48	503	27.41
Retro-orbital pain		265	20.14	130	23.13	184	12.02	25	10.59	14	33.33	241	13.13
Vomiting		424	32.22	208	37.01	162	10.58	25	10.59	17	40.48	518	28.21
Nausea		467	35.49	229	40.75	140	9.14	52	22.03	20	47.62	559	30.45
Diarrhoea		299	22.72	166	29.54	145	9.47	32	13.56	13	30.95	326	17.76
Abdominal pain		307	23.33	165	29.36	387	25.28	14	0.06	18	42.86	328	17.86
Bleeding		174	13.22	91	16.19	188	12.28	7	2.97	29	69.05	174	9.48
Right hypochondrial tenderness		356	17.33	317	56.41	550	35.92	27	11.44	24	57.14	480	26.14
Epigastric tenderness		228	17.33	121	21.53	290	18.94	16	6.78	9	21.43	298	16.23

Table 3. Biochemical characteristics of the patients classified according to the 1997 and 2009 WHO dengue case definitions.

	1997 Classification [a]				Dengue with warning signs [b]				Severe dengue [c]			
	DF (N = 1,316)		DHF (N = 562)		Yes (N = 1,647)		No (N = 231)		Yes (N = 41)		No (N = 1,837)	
	N	%	N	%	N	%	N	%	N	%	N	%
Lowest WBC (Mean±SD) × 10^9 / L	3.48[a]	1.55	3.39[a]	1.61	3.40[b]	1.58	3.99[b]	1.62	2.91[c]	1.3426	3.23[c]	1.54
0-2	238	18.09	144	25.62	366	22.22	25	11.02	13	31.72	331	18.01
2.01-4	752	57.14	301	53.56	888	53.91	129	55.93	24	58.53	1,098	59.78
> 4	326	24.77	117	20.82	393	23.87	77	33.05	4	9.75	408	22.21
Lowest Platelet (Mean ± SD) /µL	86[d]	46	27[d]	20	57[e]	34	129[e]	35	23[f]	18	67[f]	42
0-25 000	149	11.18	358	63.69	481	29.20	4	1.72	27	63.87	456	24.89
26-50 000	257	19.57	134	23.79	375	22.76	5	2.15	11	26.82	378	20.63
51-75 000	307	23.38	44	7.87	348	21.12	15	6.87	2	4.87	369	20.24
76 -100 000	299	22.72	22	3.94	322	19.55	20	9.01	1	4.44	326	17.32
> 100 000	304	23.15	4	0.72	121	7.37	187	80.26	0	0.00	308	16.81
Highest AST (Mean ± SD) IU/ L	102.89[g]	77.92	142.44[g]	106.54	110.59[h]	96.43	68.42[h]	47.00	166.83[i]	128.13	100.97[i]	84.09
Mild	595	88.27	257	81.33	566	83.72	74	77.89	23	71.87	828	86.43
Moderate	71	10.53	47	14.87	77	11.39	18	18.94	7	21.87	91	9.49
Marked	8	1.20	12	3.80	33	4.92	3	3.17	2	6.26	39	4.11
Highest ALT (Mean ± SD) IU/ L	68.33[j]	62.61	88.34[j]	86.62	74.90[k]	71.16	52.91[k]	42.43	84.84[p]	83.21	72.84[p]	68.40
Mild	541	86.97	231	81.05	500	82.78	74	80.43	20	76.92	748	84.71
Moderate	71	11.41	47	16.49	87	14.40	16	17.39	4	15.38	114	12.91
Marked	10	1.62	7	2.46	17	2.82	2	2.18	2	7.70	21	2.38
Haematocrit drop of more than 5% from the baseline	75	5.69	99	17.61	149	9.73	10	4.23	6	14.28	165	8.98

1. Lowest WBC (Mean±SD) x 10^9 / L [t-test]: [a]P = 0.24; [b]P = 0.001; [c]P = 0.03; 2. Lowest Platelet (Mean±SD) /µL [t-test]: [d]P = 0.01; [e]P = 0.01; [f]P = 0.02; 3. Highest AST (Mean±SD) IU/ L [t-test]: [g]P = 0.01; [h]P = 0.01; [i]P = 0.03; 4. Highest ALT (Mean±SD) IU/ L [t-test]: [j]P = 0.01; [k]P = 0.01; [p]P = 0.02.

Of the 3 cases with DF classified as SD, 1 had massive bleeding and 2 had acute kidney injury and were classified as severe dengue. All three patients had regular ultrasound scans to look for leakage and were negative and none received non-steroidal anti-inflammatory drugs. In the 30 cases with severe bleeding which includes 1 with organ failure, the mean haematocrit on admission was 41 (range: 33-49) and on discharge was 42 (range 36-48). The mean highest haematocrit during the course of the illness was 45 (range: 38-50). Regarding the eight DHF-3 patients: the median day of admission was day 3 (range: day 3-5) and the median length of time between admission and shock was 48 hours (range: 0-72 hours). Two patients were admitted with shock and were successfully resuscitated. Of the 4 cases with organ failure, 3 had acute kidney injury with maximum creatinine ranging from 210-240 micromol/L and the values returned to normal with recovery. One patient had myocarditis which resolved with recovery. There was elevated troponin I with T inversions in electrocardiogram but the two dimensional echocardiogram was normal. The liver enzymes and coagulogram were normal 3 patients. One patient with severe bleeding had normal liver enzymes and increased prothrombin time with an international normalised ratio (INR) of 1.7.

Tables 2 and 3 outline the clinical and investigation findings of patients classified according to the two dengue case classifications. Clinical features such as headache ($p = 0.004$), retro-orbital pain ($p = 0.008$), vomiting ($p < 0.001$), abdominal pain ($p < 0.001$), abdominal tenderness ($p < 0.001$), bleeding manifestations ($p < 0.001$) and investigation findings such as lowest platelet count ($p < 0.001$), lowest white blood cell count ($p = 0.028$), highest alanine transaminase (ALT) level ($p = 0.003$) and highest aspartate transaminase (AST) level ($p < 0.001$) were all associated with DHF compared to DF. Furthermore, clinical findings such as retro-orbital pain ($p = 0.003$), abdominal pain ($p < 0.001$), abdominal tenderness ($p < 0.001$) and bleeding manifestations ($p < 0.001$) and investigation findings such as lowest platelet count ($p < 0.001$) and highest AST level ($p = 0.006$) were associated with severe dengue. The level of agreement between the two dengue case classification systems were poor (Kappa = -0.035, $p < 0.001$). The mean duration of hospitalization was significantly higher in the severe dengue patients compared to DHF patients (5.4 days vs. 4.8 days, $p < 0.001$). Table 4 shows the relationship between the number of warning signs according to the 2009 WHO DCC with DF/DHF and severe dengue. As the number of warning signs increased, the proportion with DHF and severe dengue increased ($p < 0.001$).

Discussion

In this study, we compared the usefulness and accuracy of the 1997 and 2009 WHO DCCs. The level of agreement between the 1997 and 2009 WHO DCC was poor. We found the 2009 WHO DCC to be better at identifying disease severity, when duration of hospitalization was considered as an indicator of disease severity. Around 31% of those with 4 warning signs had severe dengue while 60% of patients with 5 or more warning signs had severe dengue (Table 3). Therefore presence of 4 or more warnings signs should alert the physician regarding the possibility of severe dengue infection. In addition, as the number of warning signs increased, the proportion with DHF and severe dengue increased, pointing to its ability to predict disease severity. A major limitation of the 1997 WHO DCC, is that it is mainly focused on plasma leakage and plasma leakage related haemodynamic instability and does not consider organ dysfunction or excessive bleeding as a marker of disease severity. Thus, patients with severe disease manifestations without evidence of plasma leakage are classified as DF cases . In our study, 3 DF patients had severe dengue due to the presence of organ dysfunction and excessive bleeding. The current study, analysed more than 1500 dengue patients from South Asia and included both adults and children. The percentage of severe dengue among the subcategories of 1997 WHO DCC, were similar in adults and children.

Table 4. Number of (WHO 2009) warning signs versus percentage of DF/DHF and severe dengue.

Number of warning signs	DF vs. DHF (1997)				p value	Severe dengue (2009)				p-value
	DF		DHF			Yes		No		
	N	%	N	%		N	%	N	%	
0	234	99.15	2	0.85	p = 0.002	0	0.00	299	100.00	p = 0.003
1	709	89.07	87	10.93		2	0.25	796	99.75	
2	329	58.13	237	41.87		8	1.48	532	98.52	
3	43	18.14	194	81.86		15	7.73	179	92.27	
4	1	2.63	37	97.37		13	30.95	29	69.05	
5 and more	0	0.00	5	100.00		3	60.00	2	40.00	

Several large scale studies have been conducted to compare the 1997 and 2009 WHO DCC. In 2011, Barniol *et al.* assessed the usefulness, applicability and user-friendliness of the 2009 WHO DCC in clinical practice and surveillance [20]. They included patients from the American, Eastern Mediterranean and South-East Asian regions and concluded that the revised 2009 WHO DCC has a high potential for facilitating dengue case management and surveillance. A recently conducted large scale study from Brazil showed that there was substantial agreement in disease classification between both 1997 and 2009 WHO DCC. However, the 2009 guidelines were more sensitive in diagnosing severe cases [11]. Studies from Indonesia and Malaysia also concluded that the 2009 revised criteria was more clinical useful [14,15]. However, the majority of the large studies were retrospective studies and were conducted in Latin America and South East Asia.

Wanigasuriya *et al.* studied a cohort of 106 adult dengue patients from Sri Lanka and found the 2009 WHO DCC to be more useful [21]. Furthermore, Bodinayake et al [22], concluded that large cohort studies were needed to validate the diagnostic yield of clinical impression and specific features for dengue, relative to the 2009 WHO DCC criteria [22]. In our study, features such as abdominal pain, bleeding manifestations, low platelet counts and high AST were significantly associated with severe dengue (Table 2). Similarly, Jayaratne *et al.* [23], found that the presence of abdominal pain, vomiting and bleeding manifestations were higher in severe dengue [23].

Our study includes patients diagnosed during the largest dengue epidemic in Sri Lanka and the clinical and biochemical characteristics of the adult sub group has been described in detail in a previous study [24]. In the present study, serological assays such as NS1 (n = 584), dengue immunoglobulins (n = 178) and molecular assays (n = 32) were done in a subset of patients due to resource limitations. A summary of these findings include dengue NS1 antigen, 552 (94.5%); dengue immunoglobulin M, 154 (86.5%); dengue immunoglobulin G, 17 (9.6%); dengue 2 virus (DEN-2), 28 (87.5%) and dengue 3 virus (DEN-3), 4 (12.5%).

In the 1997 WHO DCC, a positive tourniquet test was considered as a bleeding manifestation and formed an important parameter in the diagnosis of DHF grade 1. However, previous studies have found the tourniquet test to be not reliable in differentiating between DF and DHF [25]. Similarly, we did not find it useful in our population with dark skinned patients where the cutaneous bleeding manifestations such as petechiae are hardly detected. Thus in our clinical practice, tourniquet test is not routinely done. Therefore in our study, the majority of patients with DHF, only three of the four 1997 WHO DCC DHF criteria were fulfilled.

Regarding the 2009 WHO DCC, dengue with warning signs – only one warning sign is enough to warrant attention of the attending physicians for immediate intervention. Waiting for 4 or 5 warning signs to develop may result in progression to a more severe disease (usually due to massive plasma leakage and shock) with complications (massive bleeding with organs failure) if prolonged shock. DSS patients are difficult to detect in inexperience doctors and nurses because almost all of them are still in good consciousness, can walk, talk and answer your questions. Furthermore, in the 2009 WHO DCC, some criteria are not strictly defined, thus leaving room for heterogeneity in their assessment. For example, in the 2009 WHO DCC, the presence of severe bleeding and severe organ dysfunction has to be evaluated by the treating physician. Thus the classification as severe dengue may differ based on clinical judgement. To overcome this limitation, more specific criteria for assessment of bleeding and organ dysfunction should be considered.

The 1997 WHO classification emphasizes on plasma leakage because it is the major pathophysiologic change that can lead to shock and complications of bleeding and organs dysfunction later [7]. If plasma leakage is detected early with proper intravenous fluid therapy, shock and complications can be prevented. Massive bleeding is more common in adults because they have underlying peptic ulcers, took NSAID and late presentation with prolonged shock. In addition, adults might also have other underlying diseases, e.g. diabetes mellitus, hypertension, heart, liver, kidney diseases that complicate dengue with more difficult in diagnosis. These massive bleeding, co-morbidity and co-infections are added to the 1997 classification as Expanded Dengue Syndrome (EDS) in WHO SEARO 2011, revised and expanded edition [8].

Dengue endemic countries are among those developing countries with resource constrained settings so diagnosis of early dengue is difficult without the use of rapid diagnostic test (NS1Ag is most practical) so all patients who present with fever and have warning signs (the following warning signs: nausea, vomiting, abdominal pain, mucosal bleeding, hepatomegaly are common non-specific signs and symptoms in other diseases in developing countries) will be diagnosed as dengue with warning signs. These patients need strict observation with medical intervention according to the WHO 2009 DCC. The result is that the number of

patients will be increase enormously, about 20 times beyond the capacity of the healthcare personnel.

The complete blood count is the simple, practical and available in all hospitals in almost all developing countries because it is the basic investigation not only for dengue but for all other diseases. Complete blood count machines can be procured easily in all dengue endemic areas. The cost of complete blood count (1-2$) is much cheaper when compare with the NS1Ag (10-15$). In addition, complete blood count (White cells, Platelet counts and Haematocrit) helps in proper intravenous fluid management in DHF/DSS cases while NS1Ag does not. In developed countries, few cases of dengue patients and NS1Ag, including PCR are available so doctors have very small number of confirmed dengue to follow and monitor.

There were 562 DHF/DSS cases (29.9%) with plasma leakage needed close monitoring while 1,316 DF patients (71.1%) need no close monitoring. While 1,647 Dengue with warning signs (87.7%) in 2009 WHO classification need close monitoring/ observation. In the other hand, 1,085 DF (57.8%) with warning signs were unnecessary monitored closely. The workload of healthcare personnel increased from 30% to 88% so the quality of work might be reduced if the personnel were exhausted with almost 3 times the workload (Table 1).

Conclusions

The 2009 WHO DCC was more useful than 1997 WHO DCC in predicting dengue disease severity as few DF patients also had SD. Furthermore, the presence of WS identified patients with SD. However, the main disadvantage of the 2009 WHO DCC is that, it is not suitable for resource limited dengue endemic countries because the lack rapid diagnostic tests for dengue and all warning signs are non-specific and can be found in many diseases in the developing countries. All patients who present with fever and warning signs will be diagnosed as dengue with warning signs and need close observation/ admission that results in case overload. The 1997 WHO DCC, approach patients directly to detect plasma leakage and bleeding. Therefore, the severe diseases will be prevented. Furthermore, Expanded Dengue Syndrome is added to the 1997 WHO DCC in WHO SEARO 2011, Revised and Expanded edition.

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Corresponding authors

Umesh Jayarajah
P.O box: 271, Department of Surgery, Faculty of Medicine, University of Colombo, Colombo 8, Sri Lanka
Tel: +94112691111
Fax: +94112691111
Email: umeshe.jaya@gmail.com

Suranjith L Seneviratne
P.O box: 271, Department of Surgery, Faculty of Medicine, University of Colombo, Colombo 8, Sri Lanka
Tel: +94112691111
Fax: +94112691111
Email: suran200@yahoo.co.uk

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