International Journal of Latest Engineering Research and Applications (IJLERA) ISSN: 2455-7137

Volume –04, Issue – 09, September 2019, PP – 21-33

Innovative Blood Pressure Assessor for Tracking Orthostatic Intolerance in Dengue

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Abstract: Postural measurement of blood pressure (BP) is performed to assess cardiac output with insufficient blood volume during orthostasis in dengue care and other disorders. Orthostatic diagnosis is practically obscure to differentiate the health state of individuals emphasizing the need for structural BP characterization. A semi-automated monitor was utilized to record BP in both standing and supine postures for 52 participants divided into three groups, 18 non-symptomatic control, 17 febrile dengue and 17 febrile non-dengue. Postural data of hemodynamic characteristics were processed as sag and surge indicators, also assumed as digits 0 and 1. Indicator variations of characteristics were progressively combined to form the orthostatic assessors BP3, BP4 and BP5. Characteristic associations were structurally significant for assessors ($p < 0.05$) capable of distinguishing diversified BP conditions. Additionally, the prediction outcome of assessors was fairly strong in detecting dengue (sensitivity, 88.2% with positive predictive value of 48.4%) but moderate in non-dengue (specificity, 54.3% with negative predictive value 90.5%). However, BP4 had its preference ranking individuals to healthy, conditional and severe segments with constructive sub-ranks and more BP details. The finding is noteworthy considering the procedure is noninvasive, simple, affordable, and conducted on a versatile disease having interrelated medical signs with other diseases. Moreover, the introduced ranking scheme can be an effective diagnostic technique for daily preventative care at home and clinics incorporating the simple BP monitor dependably in normal and ambulatory circumstances.

Keywords: Blood pressure, febrile dengue, hypotension, orthostatic intolerance, postural measurement.

I. Introduction

DENGUE fever (DF) is a viral infection which attacks the cellular integrity of different body cells such as platelet, endothelia, mononuclear and hepatocyte. There are four serotypes identified in the tropical and subtropical regions,known as DEN1-4 viruses all under a subgroup belonging to the *flaviviridae* family [1], [2]. Dengue is on the rise and affected countries has increased from 9 to 100 countries to put about 2.5 billion of the world's populations at risk [1], [3]–[5]. According to a recent report by the World Health Organization (WHO) in the Western Pacific Region, dengue fatality rate in Malaysia has folded to 157% in 2019 from the previous year [6] and the Ministry of Health Malaysia has recently adopted the Wolbachia trials, initiated by the World Mosquito Program, to curb the widespread in some endemic areas [7]. There has been no new dengue guidelines and according to an existing release and frequent updates by WHO, the disease has been classified as a non-severe dengue fever with or without warning signs and severe dengue fever with plasma leakage, hemorrhage and organ impairment [1]. DF is accompanied with different symptoms and those common to all dengue patients are high fever, severe headache, vomiting, dehydration and plasma leakage, and the rare are severe conditions such as bleeding and organ failure. Hence, dengue diagnosis can be a challenge because it can easily be misinterpreted because it shares many symptoms with other infectious diseases such as influenza, measles, adenoviruses, acute human immunodeficiency virus (HIV), as well as food poisoning [8], [9]. There is no specific therapy for DF but can be effectively treated by intravenous fluid therapy, pain relief medication and internal bleeding management [9], [10].

Orthostatic or postural intolerance (OI), is a medical condition usually indicated to people experiencing a blood pressure sag, systolic in particular, while counteracting upright stance from supine [11]. A person with systolic drop of 20 mmHg or diastolic drop of 10 mmHg during standing is usually referred to as clinical orthostatic hypotension (OH) [11], [12]. Nonetheless, OH is also diagnosed as a subclinical disorder being relevant to various pathophysiologies and diagnosed differently depending on the type of disease, BP decline and severity. Pathological and physiological causes associated with OI are broad including heart diseases, hypovolaemia, dehydration and associated pathophysiologies, autonomic failure, neurological, neuropsychological factors, aging population, impaired cognitive function and associated disorders, pregnancy, sleeping, resting and exercise [11], [13]. BP-related OI can be accompanied with many symptoms such as sluggishness, fatigue, lightheaded feeling, confusion, blurry vision, dizziness and syncope in OH and worst scenario case [11]. This illness is also age related and elderly people with over 60 years of age have more OH

tendencies [14], [15].Despite that those in 30-39 years of age still reported significance but the worst hypotensive ones have been reported in senior persons of 80 years old and above [16].

DF is a systemic and dynamic viral disease progresses from mild febrile illness accompanied with non-specific symptoms to acute with compensated shock due to blood volume loss and blood pressure drop that may worsen due to profound shock [1], [17]. OH has been reported as a potential early predictor in DF due to dehydration, inner plasma leakage and possible hemorrhage in severe condition [18], [19]. DF-related OI is accompanied with hypovolaemia (blood loss) and insufficient blood supply affecting stroke volume and cardiac pulses. It causes BP drop and weak blood flow, and in turn imposing a crucial blood reduction in the upper extremity with orthostasis. The circulation unrest leads to hypotension symptoms, which varies in regards to disease complication and BP condition [20], [21]. The subclinical hypotension in dengue can be considered as a more severe condition than the general clinical OH, which was defined as systolic pressure of <90 mmHg, mean arterial pressure of >70 mmHg and/or postural systolic decrease of >40 mmHg with the experience of dizziness [1]. The compensated shock is referred to DF patient with normal systolic pressure, rising diastolic pressure, narrowing pulse pressure (<20 mmHg drop) and dizziness [1], [18]. On the other hand, the decompensated or hypotensive shock is recognized if DF patient has narrowed pulse pressure (>20 mmHg drop), severe OH and both systolic and diastolic pressures continue to sag until becoming undetectable [1], [17]. Moreover, the prolonged shock should also be considered as an earlier sign of hypotension and the more narrowed drop of pulse pressure (>20 mmHg) should be considered as a more severe shock and usually a strong sign of bleeding complication [17]. In a recent study, the postural fall was recognized significant if orthostasis was accompanied with systolic decline of ≥20 mmHg or diastolic decline of ≥10 mmHg, tachycardia rise of ≥30 beat/minute or hypotension symptoms such as dizziness [22].

BP is a critical hemodynamic function for smoothly moving fluid and food supplies through the blood to more dense body structures [23]. The stroke volume and cardiac pulse besides arterial walls are determinants that play key roles in regulating BP and forming the two pressure forces: systolic associated with the cardiac pulse and stroke volume, and diastolic associated with the arterial pressure during heart rest between pulses. Heart rate (HR) is the cardiac output duration taken place between two heart contractions for exerting oxygenated blood to the arterial network. The hemodynamic parameters of BP and HR are associated with circulatory in regulating efficient transport mechanism and body physiologic [24]. They should be continuously monitored for critically ill patients as well as healthy personnel to check blood circulation and tissue perfusion, also to prevent any shock syndrome [25]. DF patients apparent to hemodynamic distress undergo an ambulatory procedure of postural measurement to examine OI using the BP monitor [18], [19]. The orthostatic response varies and BP may take seconds to a few minutes to adjust depending on the health condition of individuals. Hencethe optimal startup time of postural test varies from seconds to 4 minutes depending on clinical applications. It was reported that the maximum drop occurs in the 30-60 second interval and BP retrieval with orthostasis is normally in 2-3 minutes [26], [27]. Moreover, reported studies also suggest 5 minute duration before starting supine and sitting BP measurement while quicker startup of 1 minute is thought sufficient to stabilize BP level before standing measurement [11], [28].

In this work, the aim was to differentiate postural variation of febrile dengue from healthy and other medical conditions. The original observation indicated that some parameters showing significant differences among investigated groups but clinically not that effective despite BP drop and dizziness were reported as strong dengue predictors. Distinctive analytical approach was then conducted and the derived observation showed orderly BP characterization in assessing various state of health in patient care. The research flow chart is illustrated in Fig. 1 begins with participants undergoing the postural test in standing and supine to record systolic BP (SBP), diastolic BP (DBP) and HR. Postural differences of these readings besides various BP-derived parameters were computed as supine subtracted from standing (standing – supine) to inspect characteristic variations in data sample. The Postural data indicated positive (dominant standing or surge) and negative values (dominant supine or sag). The characteristic sag and surge were recoded as 0 and 1 indicators to ease the orthostatic assessor design. A few assessor models were progressively configured searching for an inclusive ranking scheme to effectively track OI tendency. Having BP assessed and symptoms recorded, a diagnostic report should be readily generated stating clearly the particular BP condition and other related information for medical personnel or clinicians to decide the suitable treatment plans.

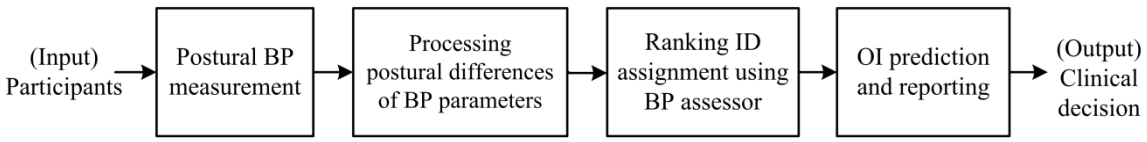

Fig. 1. Flowchart of postural BP measurement, processing and assessment

The semi-auto Omron HEM-7120 BP Monitor (OMRON Corporation) was used to measure the intended characteristics. Standard statistics of mean, median interquartile range, standard deviation, normality, skewness and kurtosis were measured to describe data sample and apply appropriate tests. Because normal and non-normal appearances were assumed in data sample, parametric and non-parametric computations were applied for inspecting correlations among parameters and differences among population groups. The IBM SPSS Software version 20 (IBM Corporation) and the MS-Excel Software version 10 (Microsoft Corporation) were utilized for data analysis and presentation. More details about the approach of this work are explained next.

II. Methodology

A. Sample size

A total of 52 participants were recruited in this work comprising three groups: 18 non-febrile control (C), 17 febrile dengue (FD) and 17 febrile non-dengue (FND). Normal volunteers having no dengue symptoms represented control.Patients with dengue symptoms in the febrile phase and being tested dengue positive represented FD. Patients with fever having non-dengue symptoms such as sore throat, coughing or running nose besides laboratory results confirming dengue negative represented FND. The control volunteers were recruited and examined at the Engineering Faculty of Universiti Kebangsaan Malaysia (UKM) in Bangi while participants in the study groups were examined either in the Public Clinic Shah Alam, Section 7 or in the UKM Medical Center in Cheras. All participants were introduced to BP measurement and clinical research and handed sufficient information in hardcopy before beginning examination. More details such as gender, age, temperature and day of illness are illustrated in Table I. Temperature and day of illness were not taken for control. The conducted measurement was part of a clinical research on investigating hemodynamics including heart rate, blood pressure and blood volume in dengue. This study was approved by the Research Ethics Committee of UKM Medical Center (MCUKM).

Table I
Information of Participants in Postural BP Measurement

Dataset				
Groups	*Count*	*Description*		
• C	18	Control group		
• FD	17	Febrile dengue		
• FND	17	Febrile non-dengue		
Total participants (N)	52			
Gender				
• Male	35	C (9), FN (14), FND (12)		
• Female	17	C (9), FN (3), FND (5)		
Age (years)	*Min*	*Max*	*Mean*	*SD*
• N (52)	19	44	28.5	±6.41
Temperature (0C)				
• FD (17)	36.8	39.3	38.5	±0.619
• FND (17)	37.7	40.0	38.5	±0.694
Days of illness				
• FD (17)	2	4	2.71	±0.588
• FND (17)	1	3	2.18	±0.529

B. Postural measurement protocol

Postural BP measurement is a recommended examination in dengue care and performed by many clinical centers [1]. The measurement session is illustrated in Fig. 2. It began by requesting participants to stand up for 3-5 minutes while wearing and fixing the pressure cuff around the left brachial arm. This standing duration before measurement was set to allow sufficient time for BP level to settle down after standing in accordance with durations reported in the literature. The start button of BP monitor was pressed afterwards to inflate the cuff and initiate the first BP reading. Depending on the condition of patients, the standing BP reading was repeated 2-3 times before requesting participant to take supine position. Similar duration of 3-5 minutes was also scheduled before supine measurement commenced to settle down BP level and take readings for 3 times.

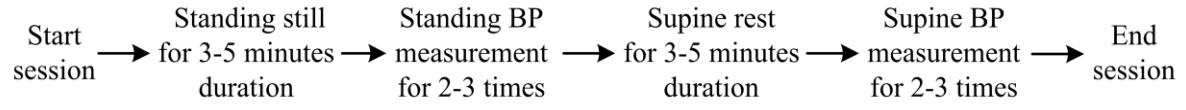

Fig. 2. Protocol of postural BP measurement

Patients having difficulties in standing up straight were asked to lean on a wall if available nearby or on the bedside with legs down and feet touching the floor surface. Weak and unrecordable BP might happen for various reasons including compensated and decompensated shocks, device limitation and malfunctioning and also conducting measurement in short duration after orthostasis especially for those with some BP condition.

Patients are usually admitted to the hospital should they complain about one or two of the warning signs such as abdominal pain or tenderness, persistent vomiting, clinical fluid accumulation, mucosal or gum bleed, restlessness, liver enlargement (>2 cm), high hematocrit and low platelets obtained from blood count [1], [29]. Medical records of study cases were carefully reviewed before measurement to adhere the set criteria including confirmed NS1 antigen positive or Enzyme-linked Immuno-Sorbent Assay (ELISA) antibody positive and onset of fever for 1-4 days. The NS1 (non-structural one) antigen and ELISA antibody are common chemical tests alternatively used depending on the day of illness to confirm dengue infection [30], [31]. Whereas control participants were introduced on a voluntary basis having no complains such as fever, dengue-like symptoms or/and any medical complaints. The medical details of each individual were entered in a case form sheet and written consents were obtained prior to investigation.

C. Processing techniques

Three clinical characteristics were recorded including the heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure (DBP). The measurement was repeated and the mean values of these parameters were determined for each individual. Additionally, the pulse pressure (BPP = SBP − DBP) and augmentation index (AI = (DBP ÷ SBP) × 100) parameters were computed to investigate BP variation in depth. Postural differences were then determined for all parameters by subtracting supine means from standing, prefixed with "up" and "dn" respectively, in line with the importance of upright stance in OI as illustrated in Table II. The absolute values (magnitudes) of SBP and DBP differences were also found essential BP characteristics. They were defined as the systole-diastole magnitude difference (ΔaSD) and the systole-diastole percent magnitude difference (%aSD). Hence for every individual, if standing data was equal or greater than that of supine (zero or positive value) then the postural variation (Δ or %) was referred as surge (dominant standing). However, if supine data was greater than that of standing (negative value) then postural variation (Δ or %) was referred as sag (dominant supine). The surge and sag interpretations were slightly different in ΔaSD and %aSD parameters. They meant that systolic postural magnitudes (|ΔSBP| and |%SBP|) are bigger (positive value) or smaller (negative value) than diastolic postural magnitudes (|ΔDBP| and |%DBP|). Moreover, the %SD parameter (%SBP –%DBP) was also introduced rather than ΔSD (ΔSBP − ΔDBP) because the latter was more like ΔBPP.

Table II
Postural Computations of Clinical Characteristics Based on Subtraction and Percent Differences

Characteristics	**Subtracted change (Δ)**	**Percent change (%)**
HR	ΔHR=upHR − dnHR	%HR=(ΔHR ÷ dnHR)×100
SBP	ΔSBP=upSBP − dnSBP	%SBP=(ΔSBP ÷ dnSBP)×100
DBP	ΔDBP=upDBP − dnDBP	%DBP=(ΔDBP ÷ dnDBP) ×100
BPP	ΔBPP = upBPP − dnBPP	%BPP=(ΔBPP ÷ dnBPP)×100
AI	ΔAI = upAI − dnAI	%AI=(ΔAI ÷ dnAI)×100
SBP-DBP	ΔaSD = |ΔSBP| – |ΔDBP|	%aSD = |%SBP| – |%DBP|

Using analysis of variances test, the characteristic differences of pre- and post-postural processing were unsatisfactory to distinguish dengue from other participants and the initial observation was clinically ineffective. A second observation was established and the core element was based on the postural trend of multiple characteristics. The derived aim was to construct a reliable diagnostic tool for assessing BP condition systematically and predict OI effectively. Postural processing presented in data sample as either positive, zero (idle) or negative values. The positive or zero values were marked as surge data (dominant standing) and the negative ones were denoted as sag data (dominant supine).The surge and sag data were transformed into 1 and 0 indicators to easily track variations of multiple parameters in setting up assessor models. Alternative parameters equivalent to investigated ones were created including sΔSBP, sΔDBP, sΔBPP, sΔAI, sΔHR, sΔaSD, s%SD and s%aSD. The prefix "s" at the beginning denoted parameters as digital (or scoring) entities in postural data. The newly minted parameters were then categorized into main and supporting parameters where sΔSBP and sΔDBP were the main ones and the other parameters were supporting. The 0 and 1 variations of multiple parameters were combined to present the ranking scheme. Combinations of setting parameters were selected in line with their correlation results to form different assessment models known as BP assessors. Investigation of models was carried to realize the appropriate setup with inclusive ranking scheme capable of organizing all BP and OI circumstances.

The assessor model construction began with inspecting the 1 and 0 patterns (sequences) in sΔSBP, sΔDBP and sΔBPP combination. These parameters were reported influential in dengue OH besides expressing strong correlation. This early attempt was known as BP3 model comprising four ranks in total, three of which conceded by the 1 and 0 variations of sΔSBP and sΔDBP. The extra rank was created due to 1 and 0 variations of sΔBPP segregating 1-1 segment of main parameters into two levels, as illustrated in Table III. The top two ranks were defined as healthy in which BP3R1 rank was healthier than BP3R2. The third rank (BP3R3) was defined as conditional BP while BP3R4 comprising 0-0 or sag-sag in main parameters was presented as severe BP towards OH. The sΔBPP introduction stalled in adding extra ranks to unhealthy segments, the BP3 model had broadly envisaged BP variations and had shortcoming in ranking scheme that excluded parameters (shaded cells of BP3 section in Table III) appeared to express further characteristic variations, and hence additional attempts were worthwhile to be considered.

The BP3 assessor was then upgraded to add 0-1patterns of sΔHR and sΔAI to combination. The upgrade constructed the 5-parameter assessor of BP5 with ranks extending to 6 in total (BP5 section of Table III). sΔHR was noticed rather idle (sΔHR=1) and retarded rank expansion due to its surge only status. On the other hand sΔAI extended the healthy and conditional segments (surge-surge and sag-sag of main parameters) into additional ranks (bold and italic fonts in BP5of Table III). This model showed better insight than BP3 showing better BP classification. Despite that this model still overlooked some BP variations that were carried out by ΔaSD and %aSD (shaded cells of BP5 section in Table III) expediting a new BP assessment model.

Table III
Postural Differences of Investigated Characteristics in Digital Form Combined Alternatively to Set UP Three BP Assessors

Ranks	**sΔSBP**	**sΔDBP**	**sΔBPP**	**sΔAI**	**sΔHR**	**sΔaSD**	**s%SD**	**s%aSD**
BP3R1	1	1	***1***	**0,1**	1	1	1	**1,0**
BP3R2	1	1	***0***	1	1	0	0	0
BP3R3	0	1	0	1	1	**0,1**	0	**0,1**
BP3R4	0	0	0	**1,0**	1	1	**0,1**	**1,0**
BP5R1	1	1	1	***0***	1	1	1	1
BP5R2	1	1	***1***	***1***	1	1	0	0
BP5R3	1	1	***0***	1	1	0	0	0
BP5R4	0	1	0	1	1	**0,1**	0	**0,1**
BP5R5	0	0	0	***1***	1	1	0	1
BP5R6	0	0	0	***0***	1	1	1	0
BP4R11	1	1	1	0	1	1	1	***1***
BP4R12	1	1	1	1	1	***1***	0	***0***
BP4R13	1	1	0	1	1	***0***	0	0
BP4R21*	0	1	0	1	1	***0***	0	0
BP4R22*	0	1	0	1	1	***1***	0	***0***
BP4R23*	0	1	0	1	1	1	0	***1***
BP4R31	0	0	0	1	1	1	0	***1***
BP4R32	0	0	0	0	1	1	1	***0***

Shaded cells indicate variation excluded in assessor setup, star marks indicate different sequencing, bold and italic fonts are expanded segments, bold and underline fonts extra variations excluded

The third assessor model was constructed in accordance with the digital indications of sΔSBP, sΔDBP, sΔaSD and s%aSD combination and known as BP4. It expanded the number of ranks to 8 in total. The 0-1 patterns of all supporting parameters were properly covered and excluded parameters had no '0, 1' instances in the BP4 section of Table III. This assessor also appeared to realize three main segments and a two-digit naming approach was implement to classify orthostatic BP into three main segments represented by sΔSBP and sΔDBP variations (left rank digit) and sub-ranks with more BP details represented by sΔaSD and s%aSD variations (right rank digit). For instance, BP4R11 is top of the list to represent the healthiest BP and matching individuals should be considered as healthy. While BP4R33 is last in the list and matching individuals should be diagnosed as serious OH. It was cautiously noticed that deterioration sequences of sΔaSD and s%aSD in the conditional segment were in other way round (ranks marked with stars in Table III) from other segments and the 1-1 sequence of sΔSD-s%SD was rather the lowest rank in the conditional segment but was top of the list in other segments. The ranking adjustment of conditional BP was made to comply with the deterioration patterns of ΔSBP and ΔDBP in this segment as illustrated in the results.

It was also realized that the surge-sag (or 1-0) instance of sΔSBP-sΔDBP was not recorded. Moreover, a sub-rank of sag-surge (or 0-1) instance of ΔaSD-%aSD was unattended by BP4 segments meaning that the negative ΔaSD or smaller systolic postural magnitude (dominant |ΔDBP|) clearly incompetent to produce positive %aSD or bigger systolicpercent magnitude (dominant |%SBP|). It is worth noting that the designated postural procedure was strictly excluded from any invasive surgical operations, new drugs or supplement intake during examinations. Furthermore, this research was systematically designed to provide the required care and safety for patients and operators, follow the latest Malaysian Guideline for Good Clinical Practice (fourth edition, 2018), and comply with the standard practice by the World Medical Association Declaration of Helsinki (2008). More findings and explanation about this work are delivered in the next section.

III. Results and Discussions

The postural measurement is an essential clinical practice for OI and the BP examination is considered as the gold standard for this test. The BP monitor was employed to record vital signs such as HR, SBP and DBP in standing and supine postures. Besides that, additional parameters such as BPP, AI, ΔaSD and %aSD were investigated to elaborate more details about BP condition. The BP readings in standing were taken a few times and then restored to supine for additional readings according to set protocol. A total of 52 participants were recruited and divided into three groups 18 of which as control (C), 17 as FD and 17 as FND. The records of data sample were organized and kept in an Excel datasheet. Standing and supine means of all parameters were first determined for individuals, groups as well as the data sample. Postural means and digital parameters (0 and 1 indicators) were also organized. A copy of overall dataset was converted into SPSS data file to convey essential data processing and analysis.

A. Introducing standing and supine datasets

Postural SBP and DBP data were plotted using Excel line chart to observe trends of individuals as illustrated in Fig. 3. A noticeable number of individuals mainly control and a few FD and FND had higher standing or narrowed up-dn SBP difference. However, the upright effect seemed to depict more cases with higher supine SBP. In contrast, DBP representingarterial pressure tend to accomplish dominant standing values due to muscle contraction with orthostasis apart from a few severe FD cases indicating higher supine DBP while the up-dn DBP differences in some FND cases were minimal.

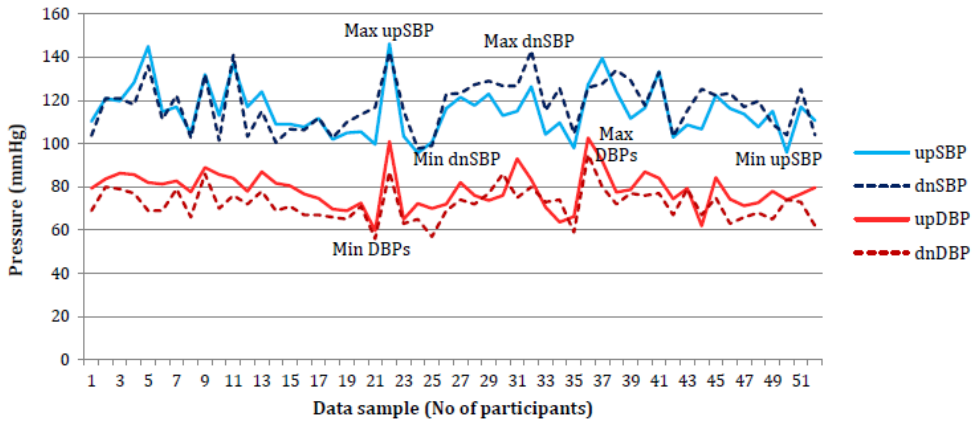

Fig. 3. Standing and supine data of SBP and DBP for 52 participants, 1 to 18 of which were controls, 19 to 35 were FDs and the rest were FNDs.

The statistics of mean and standard deviation were estimated for normally distributed data, and median interquartile range (IQR) for non-normal data, as illustrated in Table IV. Most investigated parameters were normally distributed apart from supine control data. Parametric tests such as the One-Way Analysis of Variances (One-Way ANOVA) and the Pearson Correlation statistical tests (IBM SPSS Statistics version 20) were conducted. Standing HR (upHR) recorded normal pulsations in control, moderately high in FD and the highest in FND. It had significant differences in C-FD and C- FND pairs but not in FD-FND. Supine HR (dnHR) seemed to drop pulsations in data sample. FND also triggered the highest pulsation in supine even though both study groups had the febrile condition. dnHR recorded highly significant among all pairs ($p < 0.05$).

Standing SBP (upSBP) had distinctive FD mean without recording any significance. In dnSBP data, mean differences of control and both FD and FND also indicated insignificance. The supine hike of cardiac output (SBP) in FD and FND could be related to both groups suffering fever. Standing DBP (upDBP) noticeably

recorded lower mean but without any significance with other groups. The excessive upDBP drop inFD might be due to the influence of dengue complication. In contrast, dnDBP means seemed to break almost even with very poor significance. The poor differences may trigger that fever sign and various illnesses looked to have seamless effect in supine. Standing BPP (upBPP) data present similar means in FD and FND while that of control looked clearly narrower indicating insignificance in all pairs. The dnBPP data recorded mean increases from standing and the biggest jumps occurred in febrile groups indicating significance in C-FD pair but not in C-FND and even worst in FD-FND. The upAI data also showed minimal mean variations indicating insignificant differences in all pairs. dnAI showed mean increase in control indicating significance in C-FD pair only.

Table IV
Characteristic Data of Standing and Supine Including Mean (STD) and Median (IQR) For Normal and Non-Normal Distribution, and Analysis of Variances (P Value, 95% CI) of Group Pairs using Tukey Post-Hoc Estimation in One-Way Anova Test

Mean(sd)/Median(IQR)	**N (52)**	**C (18)**	**FD (17)**	**FND (17)**
upHR	101.8(±22.2)	82.2(±14.3)	106.5(±19.4)	**117.9(±15.5)**
dnHR	85.2(±19.5)	73.5(62.7, 78)	84.2(±19.3)	**102.1(±13.3)**
upSBP	115.3(±11.8)	117.9(±11.6)	**111.8(±12.8)**	115.8(±10.6)
dnSBP	117.9(±11.9)	111.7(103.3, 121)	120(±12.9)	119.8(±9.9)
upDBP	78.5(±8.8)	81.4(±4.8)	**74.5(±10.5)**	79.3(±9)
dnDBP	72.1(±7.7)	70.1(68.5, 78.3)	70.7(±9.2)	72.8(±8.1)
upBPP	36.8(±8.3)	**33.8(31, 39)**	37.4(±7.7)	36.5(±8.3)
dnBPP	45.9(±9.6)	**39.8(36, 43)**	49.2(±7.7)	47(±9.8)
upAI	68.2(±5.5)	69.4(±4.8)	66.6(±5.7)	68.6(±5.9)
dnAI	61.3(±5.7)	65.1(63.3, 66.6)	59(±4.6)	60.9(±6.4)
Analysis of variances	**N**	**C-FD**	**C-FND**	**FD-FND**
upHR	<0.001	***<0.001, (-37.8, -10.8)***	***<0.001, (-49.2, -22.1)***	0.122, (-25.0, 2.4)
dnHR	<0.001	***0.019, (-25.9, -2.0)***	***<0.001, (-43.9, -20.0)***	***0.002, (-30.1, -5.8)***
upSBP	0.309	0.286, (-3.5, 15.8)	0.859, (-7.5, 11.7)	0.586, (-13.8, 5.8)
dnSBP	0.28	0.342, (-15.4, 4.0)	0.363, (-15.2, 4.2)	0.999, (-9.7, 10.0)
upDBP	0.054	0.48, (0.1, 13.8)	0.746, (-4.8, 9.0)	0.222, (-11.8, 2.1)
dnDBP	0.692	0.744, (-4.4, 8.3)	0.999, (-6.5, 6.3)	0.728, (-8.5, 4.4)
upBPP	0.946	0.955, (-7.8, 6.1)	1, (-6.9, 6.94)	0.955, (-6.2, 7.9)
dnBPP	0.05	***0.047, (-15.2 -0.1)***	0.203, (-12.9, 2.1)	0.766, (-5.4, 9.9)
upAI	0.319	0.305, (-1.7, 7.2)	0.906, (-3.7, 5.2)	0.548, (-6.5, 2.6)
dnAI	0.03	***0.024, (0.6, 9.3)***	0.231, (-1.4, 7.4)	0.550, (-6.4, 2.5)

The parametric correlation analysis was conducted for both standing and supine data showing upHR to have poor correlations with BP parameters ($r < 0.1$) while upSBP had stronger associations with upDBP and upBPP parameters ($r = 0.7$) but weaker with upHR and upAI. Besides that upDBP was also moderately associated with upAI ($r = 0.5$) while upBPP recorded strong inverse correlation with upAI ($r = -0.9$). Nonetheless, dnHR was still weakly related to BP parameters while the strong associations of upSBP with upDBP dropped a bit in dnSBP with dnDBP ($r = 0.6$) but increased with dnBPP ($r = 0.8$). Additionally dnSBP improved the inverse relationship with dnAI to moderate level ($r = -0.4$) despite recording weaker upSBP-upAI correlation ($r = -0.3$). Furthermore dnDBP and dnBPP maintained moderate and strong inverse associations with dnAI ($r = 0.5, -0.9$) besides their strengths with dnSBP. All standing data had strong positive correlations with their supine counterparts ($r = 0.7$ to 0.9) where upHR-dnHR recorded the highest correlation and upAI-dnAI the lowest. Despite having a few non-linear data, the non-parametric tests such as Spearman ranking correlation and Kruskal Wallis difference were also conducted due to the normality mix-up and insignificant difference was reported between parametric and non-parametric analysis, and hence the latter analysis were endorsed in this work.

B. Postural difference data descriptive

Postural data (standing – supine) was plotted using the SPSS graphical drop-line tool (IBM SPSS STATISTICS version 20), as shown in Fig. 4. A three-parameter plot illustrated standing and supine means besides postural values of data sample (N) and C, FD and FND groups. It indicated that HR, DBP and AI similarly had dominant standing means contradicting with SBP and BPP of dominant supine means except SBP mean of control. The FD data distinctively prompted big standing-supine gaps in HR, SBP and BPP (marked green), small in DBP (marked red) and unnoticed between FD and FND in AI (marked dash red).

Similar statistical measures were determined for postural data adding to case counts of dominant postures. The normality test indicated that almost all postural values of data samples and groups were normally distributed ($\rho > 0.05$) apart from overall ΔHR and ΔAI data, and also ΔBPP data of FD. The skewness and kurtosis results showed that most distribution skewed slightly to the right having positive values(0.1-1.3). Whereas, some group data slightly skewed to left having negative value (0.01-1.4). On the other hand, kurtosis results indicated that most data had sharper shapes rather than normally bent curve (0.15-3.1). A number of groups had flatter peaks and negative values in 0.01-1.1 range. The postural data recorded poor correlations for ΔHR with ΔSBP, ΔDBP, ΔBPP and ΔAI ($r = -0.3, -0.1, -0.4$ and 0.3, respectively). On the other hand, ΔSBP correlated strongly with ΔDBP and ΔBPP ($r = 0.7$ and 0.6). Moreover, ΔAI was associated poorly with ΔHR and ΔSBP ($r = 0.3$ and -0.2), moderately with ΔDBP ($r = 0.4$) and inversely strong with ΔBPP ($r = -0.8$).

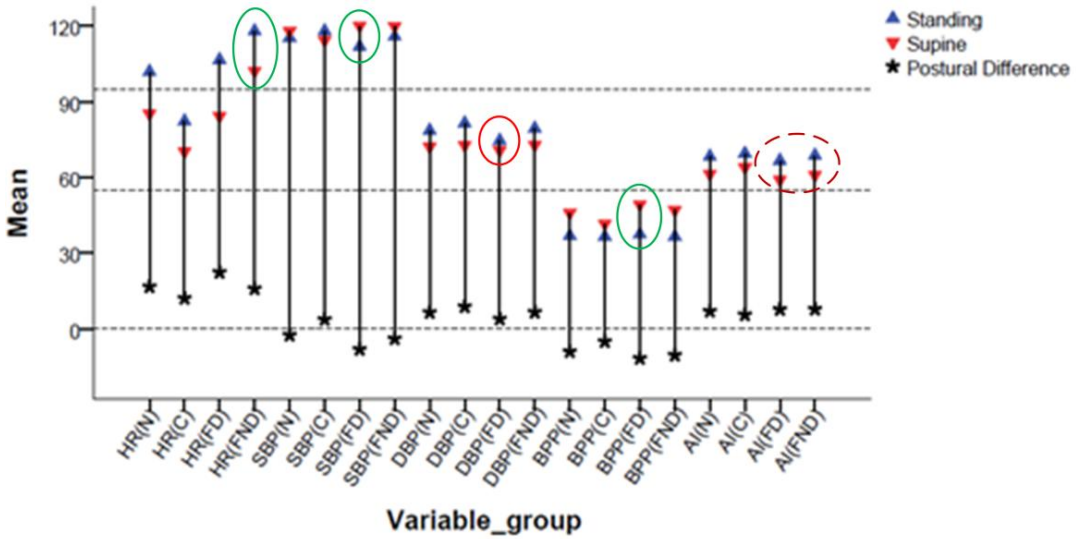

Fig. 4. Three-line plot presenting standing, supine and postural difference of HR, SBP, DBP, BPP, and AI in data sample (N) and groups (C, FD and FND).

Table V depicts the determined statistics of postural data. All individuals presented dominant standing for ΔHR and the highest variation was recorded by FD data despite both upHR and dnHR means of FD were actually moderate (Table IV). ΔHR estimated significant difference in data sample ($p = 0.005$) and C-FD pair only. ΔSBP showed dominant supine which mainly accumulated by febrile groups and FD recorded the least postural value (highest magnitude or absolute value). Despite that the lowest sag of ΔSBP was recorded at 18.7 mmHg by an FND individual meaning that no OH cases in ΔSBP data according to literature. The least ΔSBPs of FND and FD secured significance in C-FD and C-FND but not in FD-FND. In contrast, ΔDBP presented more dominant standing cases and a few FD cases only indicating otherwise these FD cases recorded a DBP drop of around 10 mmHg meaning OH condition according to literature. The narrowest ΔDBP of FD obtained significance in C-FD pair only.

ΔBPP was clearly affected with orthostasis (dominant supine) apart from a few healthy individuals of C group. The BPP drops in FD and FND were almost the same recording bigger sag (smaller negative values) from control. These sags presented significance in C-FD and C-FND pairs but none in FD-FND. Referring to [1], two cases recorded narrowed BPP with orthostasis dropping within decompensated shock margin (> 20 mmHg). Whereas, three cases (1 FD and 2 FNDs) estimated narrowing orthostatic BPP and fluctuated within the compensated shock margin (< 20 mmHg). Most cases of serious BPP drop had higher and serious SBP sag while DBP was still surging with orthostasis. Conversely, ΔAI increased in upright stance apart from a few cases (one control and two FDs) indicated otherwise. The AI hike recorded insignificance in data sample and all pairs. The AI hikes of FD and FNDwere almost similar recording bigger surge from control. The relationship between ΔBPP and ΔAI seemed reverse due to the fact that the former determined from subtraction (SBP – DBP) while the latter was oppositely derived from division (DBP ÷ SBP). Despite AI not being investigated in dengue, a single FD case could be rated as serious having distinctive AI rise (> 20%).

The characteristic analysis of pre- and post-postural data gave essential information about dengue pathophysiology. However, we noticed that characteristic differences were mostly significant in C-FD and C-FND pairs but not in FD-FND pair. Hence, the postural BP test was ineffective clinically to distinguish dengue from FND individuals, and may in turn implicate in deciding the suitable treatment plan.

Table V
Postural Data Including Counts, Mean (STD) and Median IQR for Normal and Non-Normal Distribution, and Analysis of Variances (P Value, 95% CI) of Group Pairs Using Tukey Post-Hoc Estimation in ANOVA Test

Count Up(Dn)	**N (52)**	**C (18)**	**FD (17)**	**FND (17)**
ΔHR	52(0)	18(0)	17(0)	17(0)
ΔSBP	21(31)	**17(1)**	**2(15)**	**2(15)**
ΔDBP	47(5)	18(0)	13(4)	16(1)
ΔBPP	3(49)	3(15)	0(17)	0(17)
ΔAI	49(3)	17(1)	15(2)	17(0)
Mean(sd)/Median(IQR)	**N (52)**	**C (18)**	**FD (17)**	**FND (17)**
ΔHR	14.8(9.8, 21.5)	12.0(±7.3)	**22.4(±11.3)**	15.8(±7.6)
ΔSBP	-2.7(±8.3)	3.7(±5.6)	**-8.1(±6.2)**	-3.9(±8.3)
ΔDBP	6.4(±6.1)	8.8(±3.8)	**3.8(±7.6)**	6.6(±5.7)
ΔBPP	-9.1(±6.1)	**-5.1(±4.7)**	-10(-13.8, -9.5)	-10.5(±4.9)
ΔAI	7.2(5, 8.9)	5.5(±3.2)	7.6(±5.4)	7.7(±2.9)
Analysis of variances	**N**	**C-FD**	**C-FND**	**FD-FND**
ΔHR	0.005	***0.003, (-17.6, -3.1)***	0.435, (-11.0, 3.5)	0.088, (-0.8, 14.0)
ΔSBP	<0.001	***<0.001, (6.2, 17.3)***	***0.005, (2.1, 13.2)***	0.182, (-9.8, 1.4)
ΔDBP	0.05	***0.039, (0.2, 9.8)***	0.518, (-2.6, 7)	0.348, (-7.7, 2.0)
ΔBPP	0.001	***0.002, (2.3, 11.3)***	***0.014, (0.9, 9.9)***	0.75, (-5.9, 3.2)
ΔAI	0.172	0.242, (-5.4, 1.1)	0.23, (-5.5, 1.0)	1, (-3.3, 3.3)

Bold and underline fonts represent distinctive data, bold and italic fonts represent significant differences.

C. Analysis of orthostatic BP assessor models

Independent analysis of investigated parameters was presented partial significance among groups but unsatisfactory for clinicians. The multi-characteristic associations were conducted to progressively construct BP3, BP5 then BP4 assessors. The 0 and 1 variations of selected characteristics shaped the model ranking schemes. The parameters constructing models were divided into main (sΔSBP and sΔDBP) and supporting (sΔBPP, sΔAI, sΔHR, sΔaSD, s%SD and s%aSD). The conditions of surge-surge (1-1), sag-surge (0-1) and sag-sag (0-0) in SBP-DBP were lately realized in the BP4 construction and expressed as healthy, conditional and severe BP segments, respectively. The assessor construction was a derived standpoint to overcome analytical pitfalls and assess orthostatic health state of investigated groups. This section covers assessor data distributions, characteristic means and trends, and verification tests.

The data sample was properly distributed in accordance with the assessor ranking schemes as illustrated in Fig. 5. Early BP3 fitted all individuals in 4 ranks starting the healthiest in BP3R1 and ending severe in BP3R4. However, it failed to clearly present the BP state into three detailed segments. On the other hand, BP5 made further division in BP segments to have 6 ranks with ΔHR and ΔAI introduction. It accordingly distributed data sample from healthy to severethrough BP5R1 to BP5R6. Despite the expansion of healthy and severe segments, BP5 fell short in fully segregating the BP state into three segments because of its inability to expand the conditional segment.

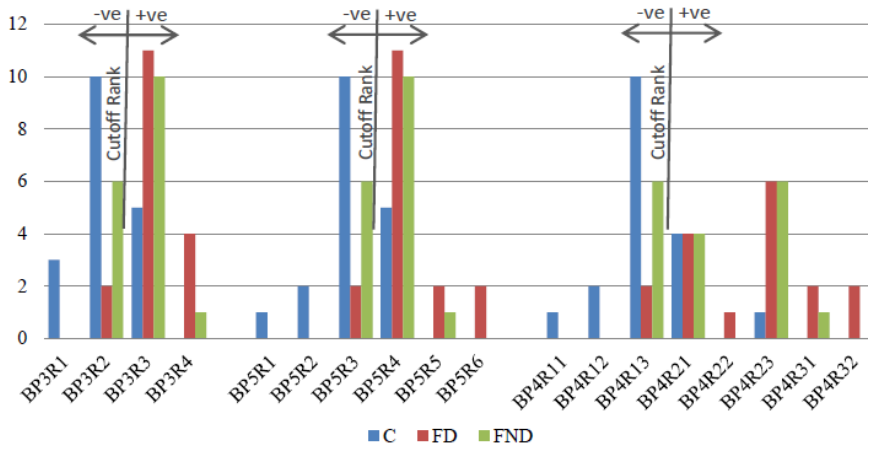

Fig. 5. Data distribution of three BP assessors with cutoff ranks equally dividing participant conditions into positive and negative.

The BP4 model made conclusive division to clearly show the BP state as three segments. The BP4 setting maintained similar division and order of ranks in healthy and severe as BP5 and expanded the conditional segment into three ranks. BP4 ranks were renamed to have two digits, one to reflect ΔSBP and ΔDBP variations and another to reflect ΔaSD and %aSD changes. Newly derived BP4R21 appeared neutral having equal distribution of four cases per group and all were marked as conditional BP. The health state was sore at BP4R22 and sorer at BP4R23 due to more systolic deterioration and lesser diastolic surge with orthostasis. It worsened in BP4R31 and the worst rated in BP4R32. Moreover, five control individuals marked in the conditional segment were unaware of having some OI signs.

The mean values were estimated to examine characteristic variations and trends in assessor ranks and plotted in Fig. 6 using the MS-Excel line tool. Most parameters had changes of courses from rise-to-fall and vice versa apart from ΔSBP presenting gradual deterioration from top to bottom ranks in all models. The BP3 model had the least line fluctuations in parameters while BP4 had the most due to the number of ranks constructing these models. ΔHR means trended distinctively agreeing with the poor correlations recorded with other parameters. In the meantime, the rank means of ΔDBP presented a single course change only recording a small surge in the healthiest rank of each model but gradually inclined in the less healthy ranks. These means dropped in the sag-surge conditional segment and continued declining to become negative with orthostasis. The ΔAI mean behaved similar to ΔDBP even though ΔAI-ΔDBP correlation was moderate (r=0.554).

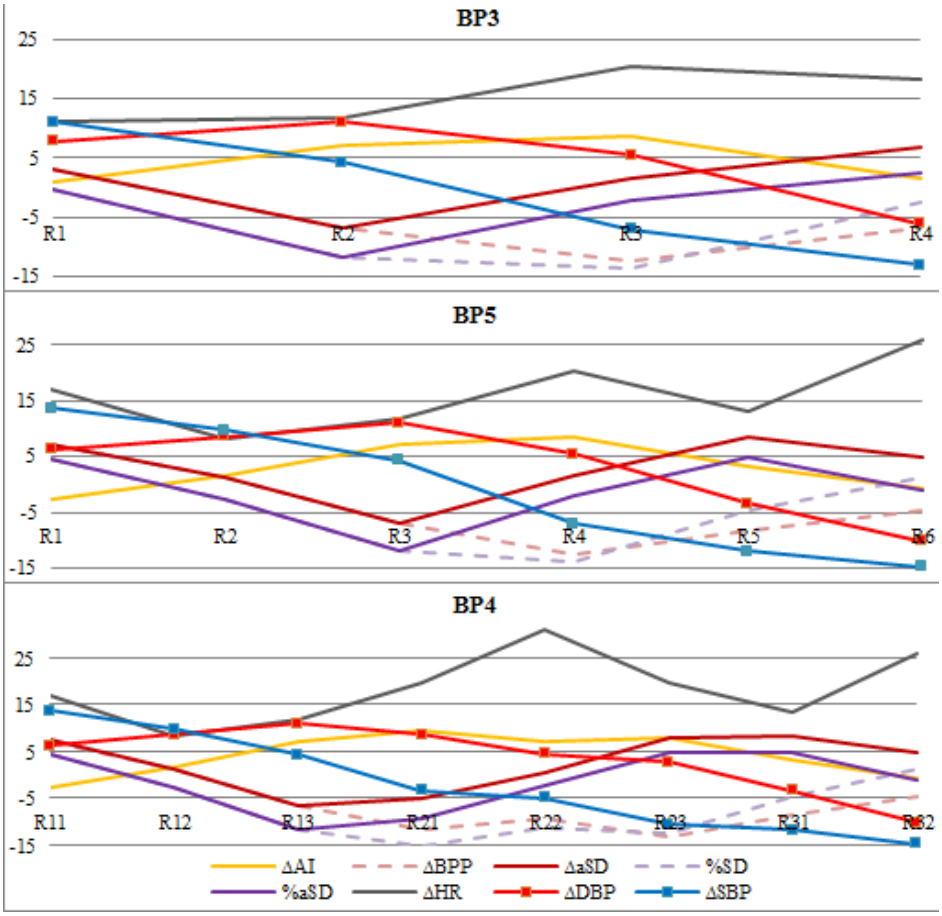

Fig. 6. Line plot to present characteristic courses within the ranking schemes of constructed assessors.

BP4 recorded ΔBPP, ΔAI and Δ%SD with three trend changes synchronized with each other. These trends seemed to follow certain patterns agreeing with correlation results of ΔAI having strong negative significance with both ΔBPP and %SD (r= −0.852 and −0.988) while ΔBPP had strong positive correlation with %SD (r = 0.829). In contrast, ΔaSD and %aSD means appeared to trend synchronously through ranks and the locations of zero crossing triggered crucial turning points in creating more ranks and BP insights. ΔaSD and %aSD marked two line changes seemed to agree with the very strong positive correlation obtained between them (r = 0.959). Furthermore, the line plot showed how ΔaSD and %aSD had rising courses in the sag-surge segment but presented declination in the surge-surge and sag-sag segments.

On the other hand, ΔBPP and %SD patterns began to trend close to each other with the former being higher before their mean differences shrank to intersect with each other in the sag-sag (or 0-0) segment to begin recording higher %SD. These parameters held similar trends as ΔaSD and %aSD in the healthy segment then started to change pattern and divert afterwards because they were sensitive to sign changes held by ΔSBP and ΔDBP which in turn affecting their outcomes unlike ΔaSD and %aSD using absolute values. We believe the line representation provided better insight about characteristic behaviors than the correlation results which the latter only indicated that ΔAI had negative association with ΔaSD,%aSD, ΔBPP and %SD rather specifying the change of course among them.

The three assessors were verified using the statistical tests of Chi-Square of independence (X^2) and prediction. To run SPSS Chi-Square test, ranks were referred as the raw categorical variable and group distributions within ranks represented the column categorical variable. These representations produced degrees of freedoms (df) equal to 6, 14 and 10 for BP3, BP4 and BP5 respectively. Assessor distributions were then weighted for discrepancy before conducting the cross-tabulation analysis. The results indicated significance for all models, BP3 ($X^2 = 18.7$, $p = 0.002$), BP4 ($X^2 = 23$, $p = 0.025$) and BP5 ($X^2 = 19.5$, $p = 0.01$), rejecting the null hypothesis and denoting characteristic associations were constructive in building assessors and arranging data sample. Despite the low significance, BP4 was the preferred model because it clearly segregated BP condition into three segments with more BP rankings and physiological details. The low significant of BP4 was related to shortages in sample size and when consolidating ranks into main segments (df = 4), the new distribution showed X^2 slightly decreased with enhanced significance ($X^2 = 16.3$, $p = 0.002$).

The assessor distributions shown in Fig. 5 were presented with borderlines to create healthy and non-healthy segmentations in accordance with dengue and estimate prediction statistics of sensitivity (Sn), specificity (Sp), positive predictive value (PPV) and negative predictive value (NPV). Despite dissimilarity in rank schemes the borderlines clearly showed that data equally distributed in models, and hence the prediction outcome was similar for all models. The required values to determine prediction were estimated including true positive (TP=15 cases), false positive (FP=16 cases), false negative (FN=2 cases) and true negative (TN=19 cases). These values were then substituted in the designated formulae to calculate Sn (88.2%), Sp (54.3%), PPV (48.4%) and NPV (90.5%). Results show that data sample well fitted in the derived ranking schemes. Sn indicated that models were highly capable of identifying dengue cases. Whereas, Sp appeared to moderately distinguish non-dengue cases. Nonetheless, the other measures indicated that about half of the positive dengue cases were truly predicted (PPV = 48.4%) while almost all negative cases were truly predicted (NPV = 90.5%). The outcomes of these diagnostic assessors were reliable taking into consideration that this work was purely based on the postural test which is simple, inexpensive and non-invasive in nature. Besides that dengue pathophysiology also implicates results because it shares many symptoms and medical signs with other illnesses. One way to weight the positive prediction is by widening the scope of setting parameters to include specific symptoms and construct a more dengue-centric assessor.

IV. Conclusions

The standing and supine data presented essential awareness about the febrile phase of dengue pathophysiology. Clinical characteristics partially distinguished dengue from normal and febrile non-dengue participants but differences were hardlysignificant especially between febrile groups. On the other hand, the associations of multiple characteristics and that of BP4 assessor in particular were more practical sorting the BP condition into healthy, conditional and severe segments. This work also emerged that BP and HR were poorly correlated and the latter was hard to predict dengue. Besides that, extra diastolic surge was exceptionally presented at certain narrow systolic surge before both turned into sag with further medical deterioration during orthostasis. The systolic-surge diastolic- sag condition was not met enlightening the importance of this association and emphasizing that any diastolic sag should be taken as a serious deterioration in BP and health. OI is a serious medical complication affecting various physiological, pathological and psychological activities of humans in our ecosystem. We totally recommend the postural BP measurement as a prime care in clinical practice and the newly minted assessor of BP4 is a potential synergy to this test. BP4 was a systematic and simple scheme to effectively rank the health state of individuals suggesting further validation and future research to advance the technique as a sound software gadget of BP-based orthostatic decision maker for wider and reliable use in patient care.

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Authors would like to thank Universiti Kebangsaan Malaysia for partly supporting this work through its Research University Grant GUP-2018-050. We would also like to thank Dr. NajibRafee for his help in data analysis and for his kind and willingness in giving essential feedback without hesitation.

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