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Application of the enhanced single face photo as a novel screening tool for diagnosis of dengue infection and influenza

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ABSTRACT

The invisible facial flushing in dengue infection and influenza can be detected and visible by the Manote and Matinun (M&M) technique using PC program and smartphone app. The unique patterns of facial flushing provide a clue to the diagnosis of dengue infection and influenza. To analyze the facial flushing areas in dengue infection and influenza compared with other causes from the single face photo by smartphone camera app and apply the enhanced single face photo as a novel screening tool for diagnosis of dengue infection and influenza. The patients with acute febrile illness were classified into 4 groups of different underlying causes as other causes, dengue, influenza A and influenza B respectively. The single face photo was enhanced with the Rock Art Enhancer app using for Android smartphone in 3 steps modified from the Manote and Matinun technique and further analyzed with the ImageJ program with Color Inspector 3D plugin. The patterns of the facial flushing areas were differentiated into 3 categories, as no facial flushing, localized facial flushing and generalized facial flushing. The analysis of the facial flushing areas was calculated in percents of primary and secondary facial flushing areas (1 FFA and 2 FFA). The sensitivity or "true positive rate" of 3 steps modified Manote and Matinun technique for all tests in dengue, influenza A and influenza B group is 96.8% (94.2% for all patients). The 97.8% of dengue group tests (94.7% for of dengue patients) could be detected the facial flushing either localized or generalized pattern. The upper cut-off points that helps distinguish from neither dengue nor influenza to either dengue or influenza is approximately 20% and 9% in the primary facial flushing areas (1 FFA) and the secondary facial flushing areas (2 FFA) respectively. Although the generalized facial flushing patterns were found in dengue (66.7%) more than in influenza (50%), but we could not distinguish between dengue and influenza, depending on two different patterns of facial flushing (no statistically significant differences, P = 0.09). The enhanced single face photo with 3 steps modified Manote & Matinun technique is useful as a novel screening tool to distinguish other causes of acute febrile illness from both dengue infection and influenza. The upper cut-off points in both primary facial flushing areas (1 FFA) and the secondary facial flushing areas (2 FFA) help for the recognition and diagnosis either dengue infection or influenza. Because it is useful and effective as well as economical and available so it should be suitable for a novel screening tool in the diagnosis of dengue infection and influenza, including for the application of telemedicine in the future.

Keywords— *Facial Flushing, Dengue infection, Influenza, Face photo, Smartphone Application, Rock Art Enhancer App, Screening tool, Telemedicine*

1. INTRODUCTION

Dengue virus (DENV) is the most common arbovirus worldwide, with >128 countries showing evidence of endemic dengue transmission and almost 4 billion people living in areas at risk of dengue infection (1). Dengue viral infections affect approximately 390 million individuals annually, of which 96 million infections manifest as apparent dengue infections (2).

Influenza is a viral respiratory disease of global importance. In fact, many experts believe that the pandemic of influenza is a threat to the health of people around the world. Influenza affects all countries, communities and individuals. Seasonal influenza viruses will continue to circulate, and influenza viruses with pandemic potential will continue to emerge (3). Influenza spread around the world in yearly outbreaks, resulting in about three to five million cases of severe illness and about 250,000 to 500,000 deaths (4).

Dengue can be diagnosed clinically and confirmed by a variety of methods, including anti-DENV antibodies, non-structural protein 1 (NS1) antigen or DENV-specific nucleic acid detection. In countries with dengue fever prevalent, but limited resources, medical providers may not be able to screen all patients presenting with acute febrile illness with the dengue NS1 antigen or dengue nucleic acid detection tests, especially if a complete blood count (CBC) performed, did not reveal the presence of leukopenia (5).

Diagnosing influenza clinically is often difficult because of the variability of symptoms and the numerous other causes of 'influenza-like illness'. An accurate result from an influenza test performed at the bedside, or within hours of presentation, may assist in diagnosis and patient management. Rapid influenza tests based on viral antigen detection with point-of-care tests and immunofluorescence may be useful for primary care clinicians (6).

In resource-poor settings where dengue is prevalent and influenza is epidemics, clinicians may be forced to rely on their clinical judgments, as accurate diagnostics tend to be expensive, time-consuming or both. Early and accurate diagnosis for both diseases is important for guiding appropriate management and guide to prompt treatments. In our previous study, we reported the two cases of dengue infection and influenza with invisible facial flushing. The invisible facial flushing can be detected and visible by the Manote and Matinun (M&M) technique using PC program and smartphone app (Decorrelation stretching and K-means clustering). The unique patterns of facial flushing in the patients with high fever provide a clue to the diagnosis of dengue infection and influenza (7).

Next, we studied the patients with acute febrile illness to evaluate the facial flushing areas using with the enhanced single face photo by smartphone camera app and analyzed with the PC program.

Thailand has a population of 69.11 million (53% are in urban areas). There are 93.61 million mobile phone users, more than the population of the whole country. There are 57 million internet users and there are up to 51 million Social Media users. Of the total internet users, there are 46 million Social Media users on a regular basis through Smart Device (8). Therefore, almost everyone in every family needs a smartphone for personal use in every area of the country.

So the enhanced face photos using the smartphone camera and the special Android app may be useful as a novel screening tool for diagnosis of dengue infection and influenza in the general population everywhere. If it is effective and practical, its applications can be used in all healthcare facilities in telemedicine following the doctor's advice, because it is economical, and readily available.

2. METHOD

Patients were retrospectively selected from the private clinic of Dr. Manote, Buriram province, Thailand from June to October 2019. The inclusion criteria consisted of men or women and boy or girl, of any age, with acute febrile illness being classified into 4 groups of different underlying causes.

Group 1 - Other causes
The underlying causes of acute febrile illness were non-dengue, non-influenza, such as bacterial infection, other viral infections e.g., Roseola infantum, herpangina, viral croup and bronchiolitis.

Group 2 - Dengue infection
Anyone with acute febrile illness who were positive for any dengue nonstructural protein 1 - NS1 antigen or dengue IgM with lateral flow rapid diagnostic tests.

Group 3 - Influenza A
Anyone with acute febrile illness who were positive for Influenza A antigen with lateral flow rapid diagnostic tests.

Group 4 - Influenza B
Anyone with acute febrile illness who were positive for Influenza B antigen with lateral flow rapid diagnostic tests.

The exclusion criteria consisted of any patients with clinical manifestations and clinical signs compatible with either dengue or influenza, but could not be confirmed diagnosis by above laboratory tests for dengue and influenza because of their limited sensitivity (gold standard tests for dengue are virus isolation or molecular methods and for influenza are reverse transcriptase polymerase chain reaction or RT-PCR).

The single face photo was obtained from every selected patient using the Android smartphone camera (Huawei nova 3e, with an integrated camera of 16 megapixels, resolution 4920 x 3264 pixels, autofocus and with the flash on, use the lowest ISO 100 setting with a good lighting) in the single face image with anteroposterior (AP) view presented in Figure 1. Some patients may be repeatedly photographed several times or several tests on different days while following up the symptoms.

Fig. 1: Example of Influenza A patient with single face photo in anteroposterior (AP) view

The single face photo was enhanced with Rock Art Enhancer app (9) using for Android smartphone in 3 steps modified from the Manote and Matinun technique.

Step 1 – 1st Decorrelation stretching picture
Decorrelation stretching the face photos with YUV color space (D.Stretch YUV) presented in Figure 2.

Fig. 2: After 1st decorrelation stretching with YUV color space

Step 2 – Color threshold Lab (instead of K-means clustering) picture
After 1st decorrelation stretching, perform color threshold in Lab color space with setting (+ Invert) presented in Figure 3.
L: 0 – 255 (L* for the lightness from black to white)
a: 0 - 138 (a* from green to red and setting 138 = +10 from midpoint 128)
b: 0 – 255 (b* from blue to yellow)

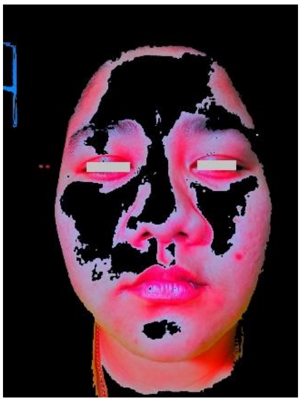

Fig. 3: After Color threshold Lab picture

With this standard setting would allow the redder areas on the face to be shown and the other areas are blackout. It would be more stable and standard than the K-means clustering.

Step 3 – 2nd Decorrelation stretching picture
Repeating decorrelation stretching again with Lab color space presented in Figure 4.

Fig. 4: After 2nd decorrelation stretching picture

The patterns of the facial flushing areas after 2nd decorrelation stretching picture were differentiated into 3 categories.
1. No facial flushing was defined as finding the red area only in the area of the lip.
2. Localized facial flushing was defined as finding any red areas in the area of the lip, nose and around the eyes.
3. Generalized facial flushing was defined as finding any red areas in the area of the lip, nose, around the eyes plus any other areas such as forehead, cheeks, chin and around the mouth.

The next procedure was to analysis of the facial flushing areas with the Manote and Matinun method. This method was calculated by the ImageJ program with Color Inspector 3D plugin (10) with, initially cropping an ellipse from Color threshold Lab picture as presented in Figure 5.

Fig. 5: Cropping an ellipse from Color threshold Lab picture (Fig. 3)

We chose Color Space: Lab, Display Mode: Histogram and the least Number of Color Cells as presented in Figure 6.

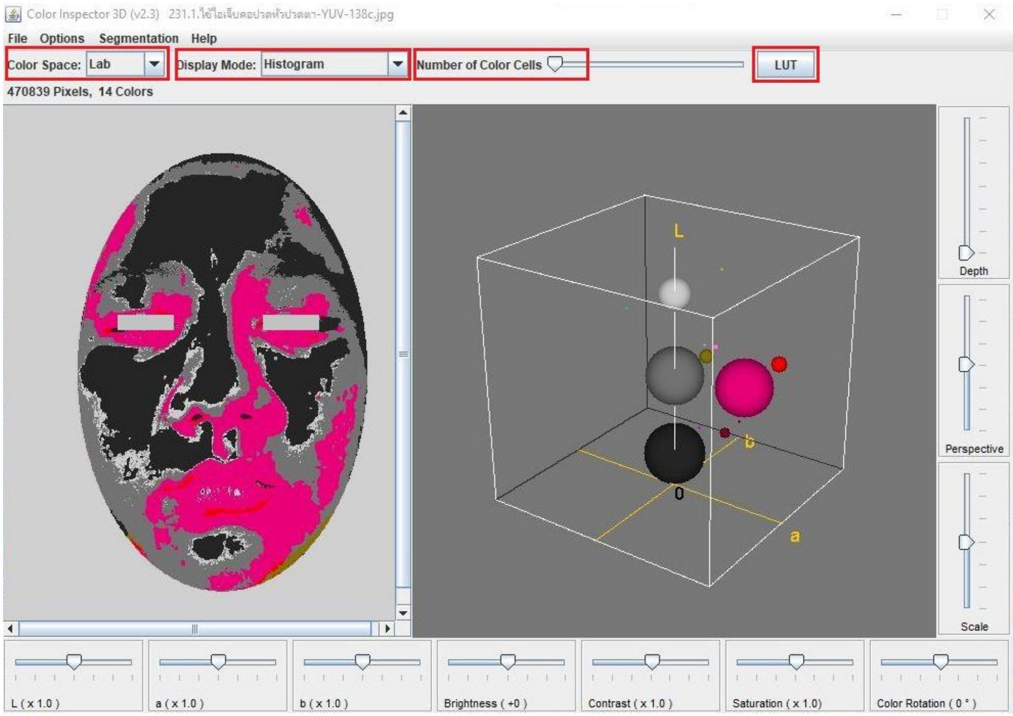

Fig. 6: Color Inspector 3D shows blackout areas and red areas

The Look Up Table (LUT) will show percentages (%) of the interested color areas in the RGB (red, green, and blue) color model expressed as an RGB triplet (r, g, b) as presented in Table 1. The primary facial flushing areas (1 FFA) were calculated from 100 – percentages of black areas (r, g, b = 37, 37, 37) as seen in the Color threshold Lab picture. The secondary facial flushing areas (2 FFA) were calculated from the sum of percentages of some red areas (r, g = 0, b) as seen in the 2nd decorrelation stretching picture.

Table 1: The Look Up Table (LUT) shows how to calculate percentages (%) of the primary facial flushing areas (1 FFA) and the secondary facial flushing areas (2 FFA)

RED	Green	Blue	Frequency	%		2 FFA
134	0	0	9	0.002		0.002
188	0	255	18	0.004		0.004
255	119	209	279	0.06		
255	130	255	2	0		
128	0	42	916	0.197		0.197
0	122	255	9	0.002		
28	210	255	5	0.001		
242	0	0	3821	0.821		0.821
135	114	0	2630	0.565		
57	36	0	1	0		
115	115	115	135587	29.12		
234	202	0	3	0		
37	37	37	177533	38.128	38.128	
233	0	120	123514	26.527		26.527
204	204	204	21291	4.573		
1 FFA					61.872	27.551

The data obtained through the modified Manote and Matinun technique and the ImageJ program with Color Inspector 3D plugin, including the primary facial flushing areas (1 FFA), the secondary facial flushing areas (2 FFA) and the patterns in the secondary facial flushing areas were compared, the differences between them being analyzed and what was essential being defined, from the enhanced single face photo, for decision-making.

3. STATISTICAL ANALYSIS

Statistical analysis was carried out using GraphPad Prism version 8.0 (GraphPad Software Inc., San Diego, CA, USA) and graphed the data. As the data were not normally distributed, one-way analysis of variance with non-parametric method in 3 groups were compared using the Kruskal-Wallis test such as the differences in percentage of facial flushing areas, both primary and secondary in 3 groups of tests in dengue, influenza A and influenza B group. The Fisher's exact test was used to analyze a 2x2 contingency table such as comparison of localized and generalized pattern between dengue, influenza A and influenza B group.

Results

3.1 Characteristics of patients and underlying causes of acute undifferentiated fever

One hundred and fifty-eight face photo tests were studied in 100 patients, 57 males, and 43 females. The mean age was 7.5 years (range: 6 months to 55 years) and the median age was 5.0 years (Interquartile range: IQR, 3.0-8.0) presented in Figure 7.

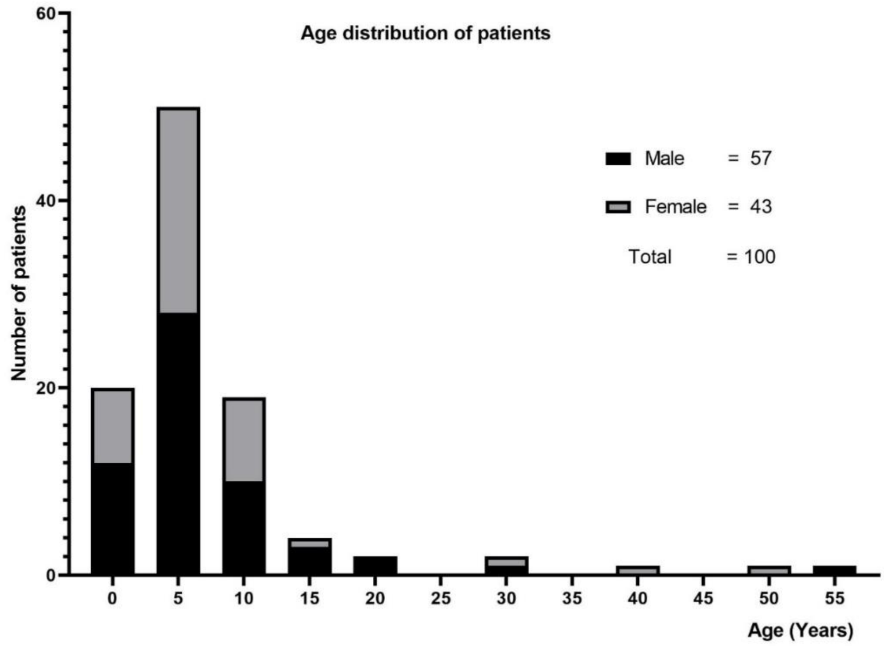

Fig. 7: Age distribution of patients

One hundred patients with acute febrile illness who were analyzed facial photos divided into 4 groups as follows: Group 1 - Other causes were 31 patients with 33 face photo tests (20.9%), Group 2 - Dengue were 19 patients with 46 face photo tests (29.1%), Group 3 - Influenza A were 33 patients with 42 face photo tests (26.6%) and Group 4 – Influenza B were 17 patients with 37 face photo tests (23.4%) presented in Figure: 8.

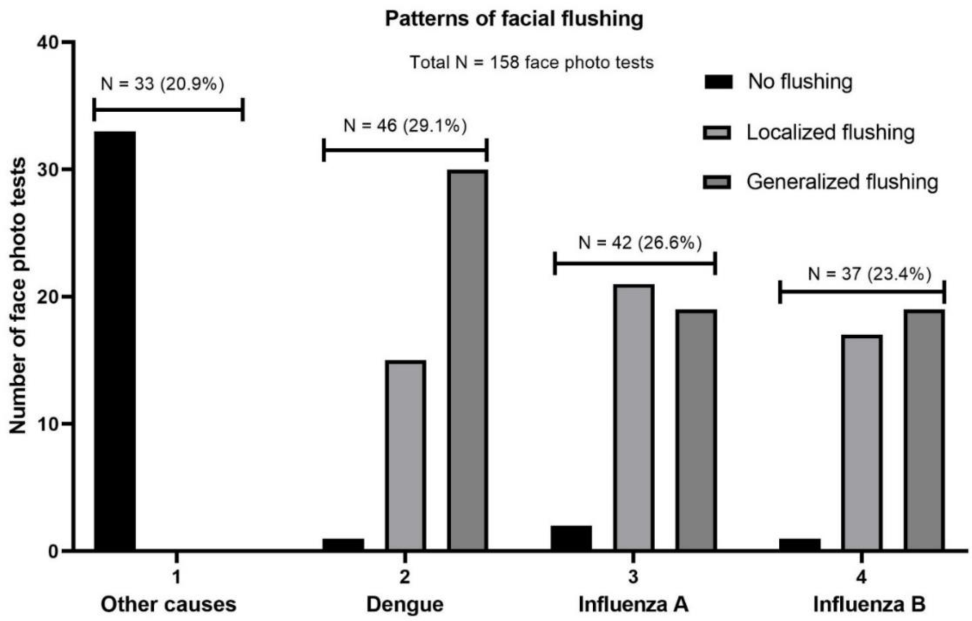

Fig. 8: Patterns of facial flushing in 4 groups of tests in different patient groups

3.2 Frequency of facial flushing patterns in each group of tests in different patient groups

In Figure 8 showed that thirty three of 37 (89.2%) of those with no flushing pattern were in the group of other causes while 4 of 40 (10.0%) of those with no flushing pattern were in group of dengue (1 case), influenza A (2 cases) and influenza B (1 case). All 4 cases in the initial no flushing pattern were changed in the pattern of either localized flushing or generalized flushing on the next day of follow up.

Forty five of 46 (97.8%) of those tests with group of dengue had facial flushing either localized or generalized pattern, whereas forty of 42 (95.2%) of those tests with group of influenza A had facial flushing either localized or generalized pattern and thirty six of 37 (97.3%) of those tests with group of influenza B had facial flushing either localized or generalized pattern.

While eighteen of 19 (94.7%) of those patients with group of dengue had facial flushing either localized or generalized pattern, whereas thirty-one of 33 (93.9%) of those tests with group of influenza A had facial flushing either localized or generalized pattern and sixteen of 17 (94.1%) of those tests with group of dengue had facial flushing either localized or generalized pattern.

When looking at the overview of dengue fever, influenza A and influenza B together, one hundred twenty one of 125 face photo tests (96.8%) had positive results or facial flushing either localized or generalized pattern.

While when looking at the overview of dengue fever, influenza A and influenza B together, sixty-five of 69 patients (94.2%) had positive results or facial flushing either localized or generalized pattern.

3.3 Percent of primary and secondary facial flushing areas in 4 different groups

Analysis the percent of the primary facial flushing areas (1 FFA %) found that higher values were in the dengue group (median, 47.2 %; IQR, 38.2 %, 56.0 %), followed by influenza B group (median, 46.1 %; IQR, 38.5 %, 50.7 %), influenza A group (median, 43.5 %; IQR, 29.7 %, 51.7 %) and group with other causes (median, 7.9 %; IQR, 6.1 %, 11.4%; 95% confidence interval [CI] 7.1 to 10.6), respectively as presented in Figure 9. The graph with bars showed the individual data points as a scatter plot and mean with range (min-max).

The maximum range of the other causes group is 26.9% while the 95th percentile of the other causes group is 19.1%. So the optimal upper cut-off points between the other causes group and the remaining groups in the primary facial flushing areas (1 FFA) is approximately 20%.

We did not find any significant differences in percent of primary facial flushing areas (1 FFA) in 3 groups of face photo tests in dengue, influenza A and influenza B group (Kruskal-Wallis test: P = 0.22 or P > 0.05).

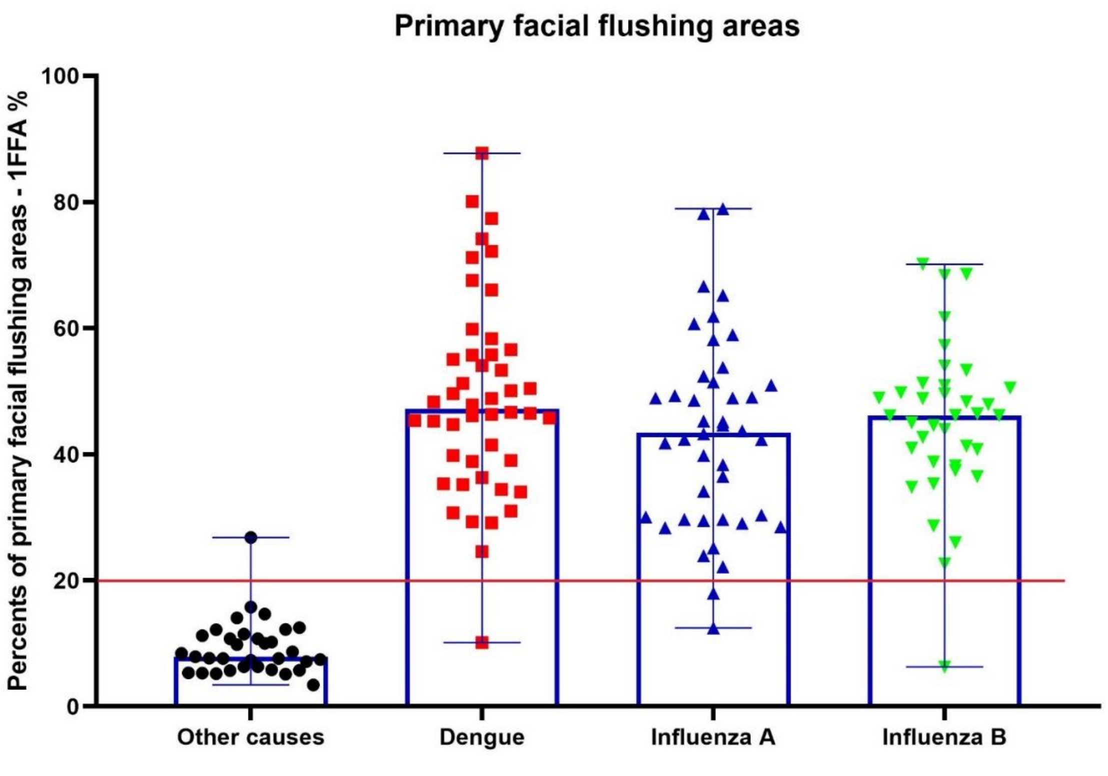

Fig. 9: Percent of primary facial flushing areas (1 FFA) in 4 groups of tests in different patient groups. The 95th percentile of the other causes group is approximately 20%

In contrast, analysis the percent of the secondary facial flushing areas (2 FFA %) found that higher values were in the influenza B group (median, 14.8 %; IQR, 10.6 %, 18.6 %) followed by dengue group (median, 12.6%; IQR, 7.2 %, 19.0 %), influenza A group (median, 11.7 %; IQR, 7.6 %, 17.1 %) and group with other causes (median, 2.6 %; IQR, 1.6, % 4.3 %; 95% confidence interval [CI] 1.7 to 3.2), respectively as presented in Figure 10.

The maximum range of the other causes group is 9.8% while the 95th percentile of the other causes group is 8.5%. So the optimal upper cut-off points between the other causes group and the remaining groups in the secondary facial flushing areas (2 FFA) is approximately 9%.

We did not find any significant differences in percents of secondary facial flushing areas (2 FFA) in groups of face photo tests in dengue, influenza A and influenza B group (Kruskal-Wallis test: P = 0.41 or P > 0.05).

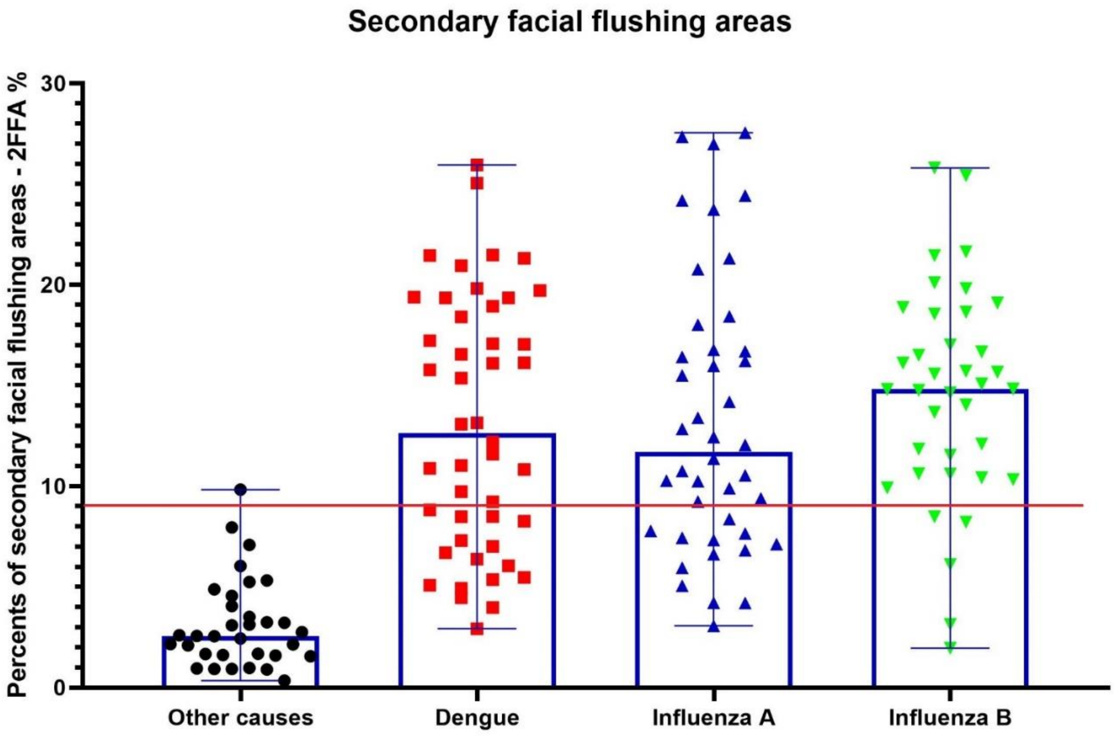

Fig. 10: Percent of secondary facial flushing areas (2 FFA) in 4 groups of tests in different patient groups. The 95th percentile of the other causes group is approximately 9%

3.4 Comparison of localized and generalized pattern between dengue, influenza A and influenza B group

In dengue group we found a generalized pattern of facial flushing more than localized pattern (66.7% and 33.3%) as well as in influenza B group (52.8 and 47.2%). In contrast, in influenza A group we found a generalized pattern of facial flushing less than the localized pattern (47.5% and 52.5 %) as presented in Figure 11.

For the influenza as a whole, we found a generalized pattern of facial flushing equal to localized pattern (50% and 50%).

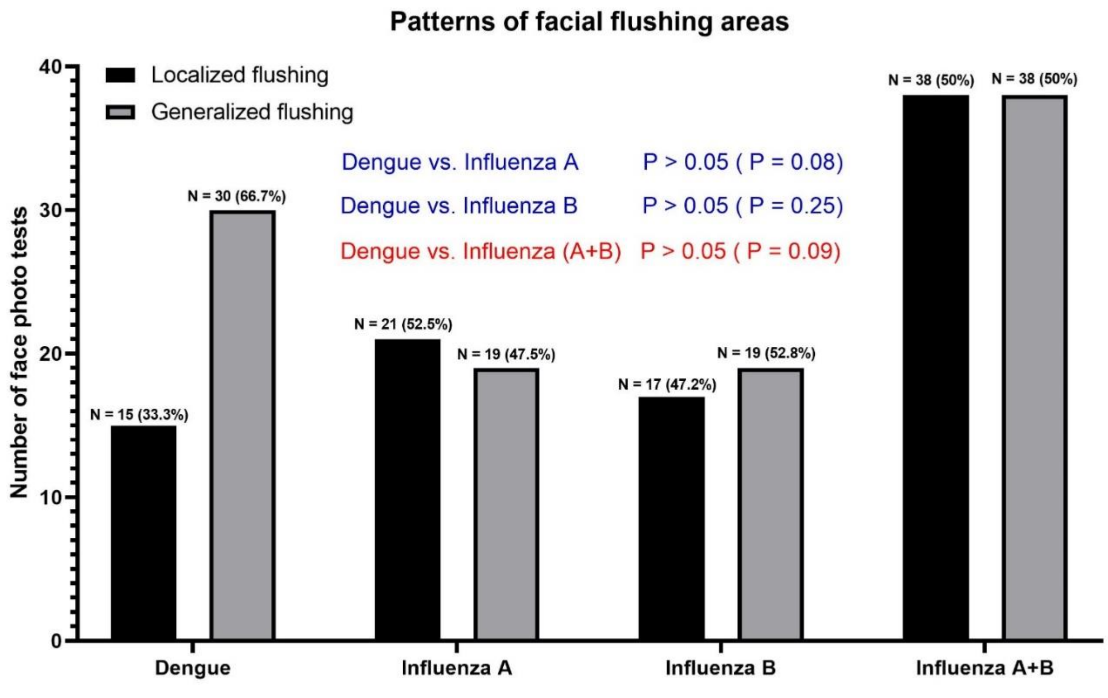

Fig. 11: Comparison of localized and generalized pattern between dengue, influenza A and influenza B group

However, there did not appear to be a difference in percents of both patterns of facial flushing in dengue group vs. influenza A group (P = 0.08) as well as in dengue group vs. influenza B group (P = 0.25) using the Fisher's exact test.

Likewise, there was no difference in percents of both patterns of facial flushing in dengue group vs. influenza group (A + B) (P = 0.09) using the Fisher's exact test.

4. DISCUSSION

Acute febrile illness or acute undifferentiated fever has frequently been reported in tropical countries. Such a disease is caused by several etiologies, principally from infection. However, clinical manifestations are generally nonspecific, such as fever, myalgia, malaise, resulting in difficulty to diagnose the actual cause of disease when relying upon patient history and physical examination solely.

In Thailand A. Leelarasamee, et al. studied acute undifferentiated fever in Thailand between 1991 and 1993 with a sample of 1,137 cases found that the etiologies in the majority (61.3%) remained unknown. The other 48.7% found that there were different causes from each area and rickettsial infection, influenza (6.0%) and dengue fever (5.7%) are the most common identifiable diseases in a tropical country like Thailand especially during the rainy season (11).

In contrast to, V. Luvira, et al. studied etiologies of acute undifferentiated febrile illness in Bangkok, Thailand between 2013 and 2015 found that dengue was the most common cause (39.6%) and influenza was the less (3.5%) (12).

With children it is often difficult to differentiate dengue from other acute febrile diseases. A study of Thai children with flushed faces and short-term undifferentiated fever diagnosed dengue in 35% of the children (13).

Facial flushing, a sensitive and specific predictor of dengue infection (14), was found in approximately half of the dengue infected patients (15). Facial flushing was also found in influenza as a physical finding (16).

In our previous report, we demonstrated that the 4 steps of Manote and Matinun (M&M) technique could detect dengue infection and influenza earlier by distinguishing unique patterns of facial flushing in the patients with high fever and could be a new tool detecting the presence of Dengue fever early on, helping prevent people from suffering potential life-threatening complications.
In this study, the single face photo was enhanced with 3 steps modified Manote and Matinun technique that is in step 2 we used color threshold Lab instead of K-means clustering because it will be more stable and standard. Image segmentation with K-means clustering used partition cluster method which depends on all the data points in the face photos including the background while color threshold Lab did not, only depend on our standard setting in L*a*b* color space.

We found that one hundred twenty-one of 125 face photo tests (96.8%) with dengue, influenza A and influenza B altogether had positive results or facial flushing either localized or generalized. While sixty-five of 69 patients (94.2%) with dengue, influenza A and influenza B altogether had positive results or facial flushing either localized or generalized pattern.

The sensitivity or "true positive rate" of 3 steps modified Manote and Matinun technique for all face photo tests in dengue, influenza A and influenza B group is 96.8% (94.2% of all patients) or approximately 97% (dengue 97.8%, influenza A and B 96.2%).

And the 97.8% of dengue group tests (94.7% of dengue patients) could be detected the facial flushing either localized or generalized pattern. If the test results are negative because it means that there is a very small chance (3%) of contracting either dengue or influenza.

The conventional tourniquet test for capillary fragility in World Health Organization (WHO 2009) dengue guidelines was used as a diagnostic sign for dengue. However, a meta-analysis of 16 studies found poor diagnostic performance, with a pooled sensitivity and specificity of 58% (95% confidence interval [CI] 43 to 71) and 71% (95% CI 60 to 80), respectively; albeit with a high level of publication bias. This poor biological correlation between dengue infection and capillary fragility may be underlying the test's poor diagnostic performance. Combined with practical considerations such as difficulty of interpretation in different skin colours and uncertainties around its positivity in other flavivirus infections, it may be time to forgo the tourniquet test as a diagnostic criterion for dengue (17).

If the initial results showed no flushing pattern, they were recommended to repeat the test on the next day of follow up. This was because all cases of both dengue and influenza with the initial no flushing pattern were shown either localized flushing or generalized flushing later on the next day. Therefore the enhanced single face photo with 3 steps modified Manote and Matinun technique is useful as a screening tool to distinguish other causes of acute febrile illness from both dengue infection and influenza. However, we are unable to differentiate the diagnosis between dengue infection from influenza. And this technique could reduce the number of patients that need to carry out an expensive laboratory test such as rapid Dengue Duo NS1 / Ab and rapid influenza diagnostic tests.

The percentages of facial flushing in dengue infection were observed varying in different studies (18) (19) and based on the naked eye.

Dr. Suneth Weerarathna, Sri Lanka, suggested that the early diagnosis of dengue infection with 1-3 days of high fever can be seen in patients with symptoms of high fever & flushed without coryza. This will help to identify dengue infection in the first 1-3 days of fever with sensitivity of 73.3 - 90.5% (20). While in this study, forty five of 46 (97.8%) of those face photo tests in group of dengue could be detected the facial flushing either localized or generalized pattern by these 3 steps modified Manote and Matinun technique.

The World Health Organization outlines that there is currently no specific treatment for dengue infection and that early detection of the disease is key to lowering fatality rates. This shows that a highly sensitive detection technique with the capability of detecting infection from the first day could have a significant impact on reducing fatalities from dengue.

The analyzed results of both the primary and secondary facial flushing areas with the Manote and Matinun method showed that
(a) The upper cut-off points of the primary facial flushing areas (1 FFA) that helps distinguish from neither dengue nor influenza to either dengue or influenza is approximately 20%.
(b) The upper cut-off points of the secondary facial flushing areas (2 FFA) that helps distinguish from neither dengue nor influenza to either dengue or influenza is approximately 9%.
(c) Although the generalized facial flushing patterns were found in dengue (66.7%) more than in influenza (50%), but we could not distinguish between dengue and influenza, depending on two different patterns of facial flushing (no statistically significant differences, P = 0.09).
(d) Although the percent of both primary and secondary facial flushing areas in 3 different groups of face photo tests in dengue, influenza A and influenza B group were different in median value and maximum range, there were also no statistically significant differences (P = 0.22 in 1 FFA, P = 0.41 in 2 FFA).

Therefore, we must distinguish dengue from influenza based on the history of living in or visiting to a dengue endemic area, including influenza exposure and clinical manifestations such as respiratory and bleeding symptoms (21). Advantages of the 3 steps modified Manote and Matinun technique and analyzed facial flushing area method.
(a) Non-contact and non-invasive, only take photos with a smartphone.
(b) Available everywhere, almost everyone in every family in the whole country or all levels of medical providers can send the face photos via the internet such as Facebook and Line app.
(c) Be useful as a screening tool for diagnosis of dengue infection and influenza and reduce the number of patients that need to carry out an expensive laboratory test.
(d) Can be the effective clues for the recognition and early diagnosis of dengue infection and influenza
(e) Interpret the findings quickly within 1 minute for 3 steps modified Manote and Matinun technique and within 5 minutes for analyzing facial flushing area method. Do not wait for half an hour to 1 hour, like waiting for the blood test or rapid influenza results
(f) Can be done repeatedly in the next 1-3 days without any pain and more economical than laboratory tests.
(g) Can be used in all healthcare facilities in telemedicine following the doctor's advice.

Therefore, this new innovative method will help all medical service providers the effective screening tool for the recognition and early diagnosis of dengue infection and influenza, especially in some health care facilities where could not be performed due to lack of laboratory support.

5. CONCLUSION

Our study demonstrated that the enhanced single face photo with 3 steps modified Manote and Matinun technique is useful as a novel screening tool for diagnosis of dengue infection and influenza because of high sensitivity, comparable to the conventional tourniquet test in World Health Organization (WHO 2009) dengue guidelines. It allows us to conclude that the presence of facial flushing pattern either generalized or localized, and in particular high percents of either the primary or secondary facial flushing areas (1 FFA or 2 FFA) more than the upper cut-off points, is a promising method for the early recognition, suggestion and diagnosis either dengue infection or influenza. We firmly believe that it should be suitable for future applications in telemedicine, especially in our country, where the distribution of medical resources to remote areas is still limited and not yet widely available.

6. CONSENT

Written informed consent was obtained from the patient for publication of accompanying images.

7. DATA AVAILABILITY

The data used to support the findings of this study are available from the corresponding author upon request.

8. ACKNOWLEDGMENTS

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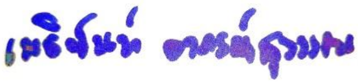

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