ORIGINAL ARTICLE

A comparison of mid upper arm circumference with other Indices for discharge from community-based management of malnutrition clinics in Jigawa State, Nigeria

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Abstract

Background: Community-based management of acute malnutrition (CMAM) program has saved millions of children with severe acute malnutrition (SAM) globally. World Health Organization recommended discharge indices include Mid-upper arm circumference (MUAC) ≥12.5cm, ≥15-20% weight gain and weight-for-height Z score (WHZ) ≥-2. We compared MUAC with WHZ and percentage weight gain as discharge criteria from CMAM.

Methods: It was a community based cohort study of children aged 6-59 months with SAM discharged from CMAM clinics in Jigawa State, Nigeria. Socio-demographic data, nutrition history and anthropometry were recorded at enrolment and discharge.

Results: Of a total of 405 children studied, 209(51.6%) were females and had a peak age group of 12-23months (43.7%, range 6-42 months). At discharge, 353(87.2%) had MUAC ≥ 12.5cm while 231(57.0%) and 204(50.4%) had percentage weight-gain ≥15% and WHZ≥-2 respectively. There was weak agreement between MUAC and WHZ (agreement 50.8%, κ=0.012) and MUAC and percent weight-gain (agreement 54.8%, κ=-0.004). Children aged between 11-23 months (OR 2.12, p=0.006) and 24-35 months (OR 2.60, p=0.002) had increased risk of discharge with inadequate percentage weight gain. WHZ <-3 at enrolment was associated with increased risk of discharge with WHZ <-3 (OR 3.21, p<0.001) and reduced risk of discharge with inadequate percentage weight gain (OR 0.45, p<0.001). Age sex, WHZ at enrollment were not associated with MUAC at discharge.

Conclusion: The use of MUAC alone as discharge criterion allows a significant proportion of children still needing urgent care exiting CMAM clinic prematurely. Stratifying these criteria may lead to better recovery before discharge.

Keywords: malnutrition, Community management of acute malnutrition, Mid upper-arm circumference, Weight-for-height Z score.

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Introduction

Severe acute malnutrition (SAM) affects over 19 million children globally with almost a million deaths annually.[1] Community-based management of acute malnutrition (CMAM) is a cost-effective program that has provided treatment for millions of children aged less than 5 years with severe acute malnutrition (SAM) in over 70 countries globally.[2,3] It employs novel innovations such as active case detection by community volunteers, outpatient therapeutic Program (OTP) for treatment with Ready-to-use therapeutic food (RUFT) of children with SAM, in-patient care in stabilization centres for complicated cases and community follow up after discharge. [2] The CMAM program is still young, hence expected to undergo several evidence-based reviews for improvement. The use of mid-upper-arm circumference (MUAC <11.5cm) as definition of SAM when compared to other definitions such as weight-for height <70% and Weight-for-height Z score (WHZ) <-3 has been widely accepted due to its simplicity and universality. Also, it has been reported to be a better predictor of death than WHZ<-3.[4] However, the use of MUAC as discharge criterion has been widely debated. In 2009, WHO recommended the use of 15-20% weight gain noticed for two consecutive weeks as a discharge criterion.[5] However, this was met with criticism because it required smaller absolute weight gain before discharge therefore leading to the early discharge of the most vulnerable children- the youngest infants with the least MUAC. [6] The use of MUAC ≥12.5cm as discharge criterion was reported to mitigate this effect and even lead to higher percentage weight gain.[7] The program guideline by Action Against Hunger which is used in Jigawa recommends the use of MUAC) at enrolment<11.5cm and ≥ 12.5cm at discharge as stand-alone criteria.[8] Another suggested index for discharge is WHZ of ≥-2 which has been reported to keep the children with the most severe malnutrition longer on treatment, hence reducing mortality.[9] MUAC of ≥12.5cm at discharge is

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said to mirror percentage weight gain of 15-20% and expected to represent WHZ>-2.[10] However, previous studies suggest that MUAC and WHZ often identify different populations of children and the use of MUAC as a stand-alone discharge criterion may exclude a population of SAM children still in urgent need of care.[11-13] Therefore, we conducted an audit of the use of MUAC≥ 12.5cm, the recommended percentage weight of ≥ 15% and WHZ≥ -2 as discharge criteria and examined associated factors.

Methods

The study was conducted in two randomly selected Local government areas (LGAs) in Jigawa State, a malnutrition high burden State, in the North West geopolitical zone of Nigeria (63.4% stunting, 40.6% underweight and 7.7% wasting amongst children aged 6-59%).[14] It has a total population of 5,787,726 (2016 Census, projected at growth rate of 2.9% per annum), with 27 LGAs, out of which 12 had CMAM programmes.[15] The study was carried out in 10 CMAM OTPs in two randomly selected LGAs (5 OTPs per LGA).

This study was nested in a larger community-based cohort study evaluating the outcome and impact of care of children managed for SAM in Jigawa State. Subjects were enrolled and discharged over a period of 5 months (June 2016-October 2016).The study population consisted of malnourished children between the ages of 6 to 59 months attending the selected OTPs. Children were enrolled into the CMAM program if they were aged 6 to 59 months with MUAC <11.5cm, had good appetite and had an identified primary caregiver. Those with medical complications were usually referred to stabilization centers. Children were discharged from CMAM if they achieved MUAC ≥12.5cm for 2 consecutive weeks or had spent a total of 8 weeks in the program. CMAM outcomes include: discharge cured (MUAC≥ 12.5cm at discharge), discharge not cured (MUAC<12.5cm at discharge), death, default (children who missed >2 consecutive weekly visits) and transfer out (transferred to stabilization centers if they developed complications after enrolment).

Using a prevalence rate of wasting of 17.7% in Jigawa State [14], power set at 90% and a confidence interval of 95%, the minimum sample size was determined to be 233. An additional 36 was added to make provision for an attrition rate of 15% (recommended minimum default rate of 15% according to the SPHERE project (Humanitarian Charter and minimum standards in humanitarian response)[16] which gave an average minimum of 27 per OTP. All consecutive consenting enrolments were included. Out of a total of 494 children enrolled, 410 were discharged. Five subjects had incomplete data so were excluded from data analysis (Figure 1).

Initial data collection was conducted during enrolment into OTPs (over a period of 4 weeks) and subsequently during discharge from OTPs (over a12 week period). Child's socio-demographic data as well as health records, immunization, feeding practices, maternal education and occupation among others were recorded at enrolment and discharge. Anthropometric variables measured included height to the nearest mm, weight to the nearest 0.1kg, MUAC to the nearest 0.1cm and presence or absence of pitting pedal oedema. WHZ, Weight-for-Age (WAZ) and Height-for-Age (WAZ) Z scores were calculated using WHO Stata zscore06 ado file. Percentage weight gain was calculated using STATA.

All data was captured on the field using CSpro, a mobile-phone based research software application (available at http://www.census.gov/ipc/www/cspro/doc.html). Developed questionnaires were uploaded unto android phones by pre-trained research assistants who were blinded to the study outcomes.

The study protocol was approved by Jigawa State Health Research Ethics Committee (JHREC/A/R/04/2016). Permission was obtained from the Jigawa Primary Health Care Development Agency as well as each LGA PHC department. A written informed consent was obtained from all caregivers. The consent forms were translated into the local language.

Data analysis was done using STATA 13 statistical package. Sociodemographic variables and discharge outcomes were presented in frequency tables. Cohen's Kappa statistic, κ was used to test for agreement between the different criteria at discharge. Generally, 0≤ k≤ 1 (although negative values do occur occasionally) with 0 signifying no agreement and 1, perfect agreement. Nominal and ordinal variables were compared using odds ratio (OR) and Pearson chi squared test(x^2). A p value <0.05 was considered significant.

Results

Of a total of 405 children studied, 209(51.6%) were females. The modal age group of the subjects was 12-23 months (43.7%) (range 6-42months) and that for their mothers was 18-25 years (51.6%). Three hundred and fifty (86.4%) were ever breastfed and 24.7% of children who were breastfed had exclusive breastfeeding. About half spent less than 8 weeks and 150 (32.7%) spent 8 weeks (range 4-12 weeks) (Table 1).

At discharge, 353(87.2%) had MUAC≥ 12.5cm, 204(50.4%) WHZ≥ -2 and 231(57.04%) percentage weight gain ≥15% (Table 2). One hundred and fifty-two (43.1%) children who were discharged having attained MUAC ≥12.5cm, failed to achieve at least 15% weight gain (Table 3). Also, 174(49.3%) children who were discharged with MUAC≥ 12.5cm still had WHZ<-2. Comparing MUAC≥12.5cm and percentage weight gain of at least 15% as discharge criteria showed 54.8% agreement which was lower than expected (55.0%). The kappa coefficient (κ) of -0.0044 demonstrated a low level of agreement between the MUAC and weight gain criteria for discharge from OTPs. Also, 50.9% agreement was observed when comparing WHZ ≥-2and MUAC≥ 12.5cm as discharge criteria which was higher than expected (50.3%). There was a low level of agreement between MUAC and WHZ discharge criteria with κ=0.012. (Table 3).

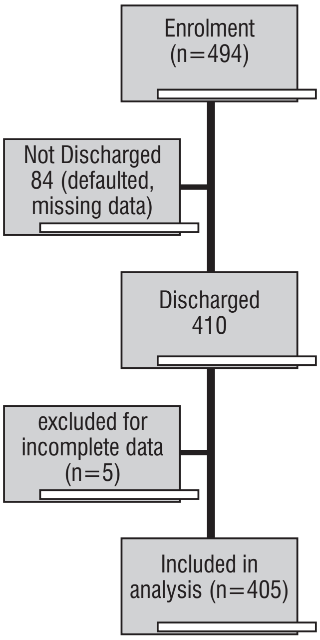

Figure 1. Flowchart demonstrating movement of subjects.

Tables 4-6 summarizes the factors associated with adverse discharge outcomes of MUAC, percentage weight gain and WHZ respectively. Age was associated with percentage weight discharge outcomes. The odds of being discharged with percentage weight gain<15% were significantly higher in children aged 12-23 months (OR 2.12, p=0.006) and 24-35 months (OR 2.60, p=0.002) when compared to those aged 6-11 months. There was no association between age and MUAC and WHZ outcomes (p>0.05). There was no association between sex and adverse discharge outcomes using MUAC (OR 1.11, p=0.729), percentage weight gain (OR=0.89, p=0.577) and WHZ (OR 0.80, p=0.255). Children who were enrolled with WHZ<-3 were more likely to be discharged with a WHZ<-2(OR 3.21, p<0.001) and less likely to be discharged with percentage weight gain<15% (OR 0.45, p<0.001). While children with treatment duration <8 weeks were less likely to be discharged with WHZ<-2 (OR 0.60, p=0.026), there was no association between duration and percentage weight gain (p>0.5) and MUAC at discharge (p>0.05).

Table 1. Sociodemographic characteristics of studied children (n=405)

Variable	Frequency (n=405)	Percentage (%)
Sex		
Female	209	51.6
Male	196	48.4
Age group (months) at enrolment		
6-11	127	31.4
12-23	177	43.7
24-35	97	24.0
36-47	4	1.0
Marital status of parents		
Married	395	97.5
Divorce/separated	9	2.2
Widowed	1	0.3
Mother's age group		
<18 years	6	1.9
18-25 years	164	51.6
26-34 years	88	27.7
≥35 years	60	18.9
Not aware	87	21.5
Number of children in household		
1-3	82	20.3
4-6	163	40.3
>6	158	39.0
Don't know	2	0.5
Type of gestation		
Singleton	376	92.8
Multiple	29	7.2
Ever Breastfed?		
Yes	350*	86.4
No	55	13.6
*Exclusively Breastfed (n=350)		
Yes	100	24.7
No	250	61.7
Duration in OTP		
< 8 weeks	208	51.5
8 weeks	130	32.2
>8 weeks	66	16.3

OTP out-patient therapeutic program

Table 2. Frequency Distribution of Discharge Outcomes

Variable	Number (n=405)	Percentage (%)
MUAC		
<12.5cm	52	12.8
≥12.5cm	353	87.2
Weight gain percentage		
< 15%	174	43.0
≥15%	231	57.0
WHZ		
< -2	201	49.6
≥ -2	204	50.4
SAM (WHZ<-3)		
Yes	125	30.9
No	280	69.1

MUAC mid upper arm circumference, WHZ weight-for-height zscore, SAM severe acute malnutrition

Table 3. Comparing degree of Agreement between Discharge Criteria using Cohen's Kappa test

variable	MUAC <12.5cm (n=52)	MUAC ≥12.5cm (n=353)	Agreement	Expected agreement	κ	z	p value
WHZ							
<-2	27	174	50.9%	50.3%	0.012	0.35	0.637
≥-2	25	179					
Weight gain percentage							
<15%	22	152	54.8%	55.0%	-0.004	-0.12	0.452
≥15%	30	201					

Std Err standard error, κ kappa coefficient, Std Err standard error, MUAC mid-upper arm circumference, WHZ weight-for-height zscore

Table 4. Association of MUAC at discharge with age-group, sex and enrolment WHZ

variable	Percentage weight gain <12.55cm (n==52)	≥12.5cm (n=353)	Odds ratio	95% CI	×2	p value
Age group (in months)						
6-11*	18	109				
12-13	20	157	077	0.37-1.63	0.557	0.456
24-35	13	84	0.94	0.40-2.15	0.027	0.869
36-47	1	3	2.02	0.04-26.60	0.364	0.470
Sex						
Male*	24	172				
female	28	181	1.11	0.59-2.08	0.120	0.729
WHZ at enrolment						
<-3	38	239	1.29	0.65-2.69	0.605	0.437
≥-3*	14	114				

*reference category, MUAC mid upper arm circumference, WHZ weight-for-height zscore, CI confidence interval.

Table 5. Association of percentage weight gain at discharge with age-group, sex and enrolment WHZ

variable	Percentage weight gain <15 % (n=174)	≥15% (n=231)	Odds ratio	95% CI	×2	p value
Age group (in months)						
6-11*	38	89				
12-13	84	93	2.12	1.27-3.53	9.607	0.006
24-35	51	46	2.60	1.44-4.68	11.814	0.002
36-47	1	3	0.78	0.01-10.10	0.046	0.995
Sex						
Male*	81	114				
female	93	117	0.89	0.59-1.35	0.311	0.577
WHZ at enrolment						
<-3	102	175	0.45	0.29-0.71	13.76	<0.001
≥-3*	72	56				

*reference category WHZ weight-for-height zscore, CI confidence interval

Table 6. Association of WHZ at discharge with age-group, sex and enrolment WHZ

variable	WHZ <-2 (n=201)	≥-2 (n=204)	Odds ratio	95% CI	×2	p value
Age group (in months)						
6-11*	56	71				
12-13	97	80	1.54	0.95-2.50	3.398	0.183
24-35	46	51	1.14	0.65-2.01	0.246	0.945
36-47	2	2	1.27	0.09-17.96	0.054	0.994
Sex						
Male*	103	93				
female	98	111	0.80	0.53-1.20	1.297	0.255
WHZ at enrolment						
<-3	162	115	3.21	2.01-5.17	27.49	<0.001
≥-3*	39	89				

*reference category, WHZ weight-for-height zscore, CI confidence interval

Discussion

In our study, 43% of the children discharged with MUAC ≥12.5cm had failed to achieve the lower limit of the previous WHO recommendation of >15% weight gain from admitting weight and demonstrated a low level of agreement between these two discharge criteria. Even though, the use of weight gain percentage has been largely criticized because it requires smaller absolute weight gain to achieve leading to shorter periods of treatment, our study demonstrates that it might actually take a longer treatment time to achieve the recommended weight gain percent than to achieve a discharge MUAC ≥12.5cm. Most of the children in this study were discharged before the recommended treatment duration of 8 weeks having attained the desired MUAC. This finding may be because the cohort of children studied were significantly older and had higher enrollment weight and may account for the difference in findings reported by Forsen *et al* where a much higher percentage (91%) of children discharged with MUAC ≥12.5cm had achieved 15% weight gain.[17] The influence of age on achieving recommended weight gain was further demonstrated by the observation that children aged 11-35 months had increased odds of being discharged not having attained expected weight gain percent when compared to children aged 6-11 months. Therefore, this raises the question whether it maybe more beneficial to use percentage weight gain as discharge criterion for older children while maintaining the use of MUAC in younger children.

About half of children discharged with MUAC <12.5cm had WHZ<-2 reflecting a poor agreement between these two discharge criteria. This confirms our earlier submission that MUAC and WHZ identify different populations of children. [11, 12] Lailou A, *et al* reported that the use of MUAC rather than WHZ missed up to 80% of children with SAM.[18]In our study, MUAC missed 105 (84% of 125) children with SAM and 69 (91% of 76) children with MAM at discharge. This also supports the recent WHO/UNICEF recommendation that the same parameter be used for admission and discharge.[19] It is however worthy to note that other studies reported better concordance between MUAC and WHZ at discharge [20] and at admission.[4] Aguaya *et al*[9], further reported that the use of MUAC reduced recovery rate by 3.5 fold and WHZ>-2 reduced recovery rate 2 fold when compared to percentage weight gain of 15%. This implies that use of either MUAC or WHZ will lead to longer duration of treatment than 15% weight gain, especially in younger children. The cost effectiveness of this finding deserves further evaluation.

In this study, while MUAC and percentage weight-gain outcomes were age-sensitive, WHZ discharge outcomes were not affected by the age of the children. This is largely because the effects of age on weight and height have been corrected for in the development of this robust anthropometric tool. There was no association found between sex and the studied discharge parameters. This differs with reports from other studies showing gender differences in anthropometry with females having lower values.[21, 22] In a systematic review, Roberfroid *et al*, reported that females were also more likely to be identified as having SAM by MUAC than males.[23] Understandably, a significant proportion of children admitted with very low WHZ did not achieve the recommended WHZ at discharge. Even though, our study did not evaluate the relationship between duration of treatment and discharge WHZ<-2, it will be worthwhile to find out if longer duration of treatment would improve outcome in the children with the lowest WHZ at admission. This may inform some form of stratification during admission as higher risk. On the other hand, children who had lower WHZ at enrolment where more likely to be discharged having achieved the desired percentage weight gain. This is because those with lower WHZ at enrolment had lower weights and required a shorter duration to achieve the necessary absolute weight gain.

Our study was limited by the fact that it was built into an operations research impact evaluation study. So, there was limited interaction with the health care providers and with caregivers at this phase of the study. Otherwise, more stringent measures will have been put in place to make sure patients met recommended program discharge criteria and to investigate reasons for poor study outcomes,

In spite of these limitations, our study provides useful evidence about non-agreeability of MUAC, percentage weight gain and WHZ discharge criteria. It also provides insight about factors to be considered when deciding on which criteria to use in sub-populations of children being treated for SAM. We therefore, recommend further studies on possible stratification in the use of these criteria in order to prevent discharging these children too early from treatment programs

Conclusion

There is poor agreement between MUAC, WHZ and percentage weight gain indices for recovery from CMAM program. The use of the new WHO recommended MUAC value as a stand-alone criterion at discharge from CMAM program leaves a significant proportion of these children exiting treatment without having recovered when evaluated using WHZ and percentage weight gain. There is a need for further studies on more appropriate discharge measures and the possibility of a stratified approach to discharge.

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References

1. Black RE, Victora CG, Walker SP, et al. Maternal and child undernutrition and overweight in low-income and middle-income countries. *Lancet* 2013; 382: 427-451. 2013/06/12. DOI: 10.1016/S0140-6736(13)60937-X.
2. UNICEF. *Evaluation of community management of acute malnutrition (CMAM):Global synthesis report*. 2013. New York: UNICEF.
3. Collins S, Dent N, Binns P, et al. Management of severe acute malnutrition. *Lancet* 2006: 368(9551);1992-2000. DOI: 10.1016/S0140-6736(06)69443-9.
4. Aguayo VM, Aneja S, Badgaiyan N, et al. Mid upper-arm

circumference is an effective tool to identify infants and young children with severe acute malnutrition in India. *Public Health Nutr* 2015; 18: 3244-3248. 2015/03/12. DOI: 10.1017/S1368980015000543.

5. WHO,UNICEF. WHO child growth standards and the identification of severe acute malnutrition in infants and children. Joint statement by UNICEF and WHO. Geneva, Switzerland 2009, p.5-6.
6. Goossens S, Bekele Y, Yun O, et al. Mid-upper arm circumference based nutrition programming: evidence for a new approach in regions with high burden of acute malnutrition. *PLoS One* 2012; 7: e49320. 2012/11/29. DOI: 10.1371/journal.pone.0049320.
7. Dale NM, Myatt M, Prudhon C, et al. Using mid-upper arm circumference to end treatment of severe acute malnutrition leads to higher weight gains in the most malnourished children. *PLoS One* 2013; 8: e55404. 2013/02/19. DOI: 10.1371/journal.pone.0055404.
8. ACF. Outpatient Therapeutic Program (OTP) refresher training for health workers: Trainers' module. Yobe: Action Against Hunger, 2011: p14.
9. Aguayo VM, Badgaiyan N and Singh K. How do the new WHO discharge criteria for the treatment of severe acute malnutrition affect the performance of therapeutic feeding programmes? New evidence from India. *Eur J Clin Nutr* 2015; 69: 509-513. 2014/09/18. DOI: 10.1038/ejcn.2014.197.
10. Burrell A, Kerac M and Nabwera H. Monitoring and discharging children being treated for severe acute malnutrition using mid-upper arm circumference: secondary data analysis from rural Gambia. *Int Health* 2017; 9: 226-233. 2017/08/16. DOI: 10.1093/inthealth/ihx022.
11. John C, Ocheke IE, Diala U, et al. Does mid upper arm circumference identify all acute malnourished 6–59 month old children, in field and clinical settings in Nigeria? *SAJCN* 2016; 1: 1-5. DOI: 10.1080/16070658.2016.1255486.
12. Myatt M, Khara T and Collins S. A review of methods to detect cases of severely malnourished children in the community for their admission into community-based therapeutic care programs. *Food Nutr Bull* 2006; 27: S7-23.
13. Myatt M, Duffield A, Sea A, et al. The effect of body shape on weight-for-height and mid-upper arm circumference based case definitions of acute malnutrition in Ethiopian children. *Ann Hum Biol* 2009; 36: 5-20.
14. NBS. Report on the nutrition and health survey of Nigeria, 2015. Abuja: National Bureau of Statistics, 2016, p. 49-55.
15. National Population Commission. All 2016 population reports by State. National Population Commission, 2017. 2018/12/04. Available online at: http//population.gov.ng/core activities/surveys/dataset/2006-phc-priority-tables.
16. SPHERE. Minimum standards in food security and nutrition. Humanitarian charter and minimum standards in humanitarian response. 2011, p. 166-169.
17. Forsen E, Tadesse E, Berhane Y, et al. Predicted implications of using percentage weight gain as single discharge criterion in management of acute malnutrition in rural southern Ethiopia. *Matern Child Nutr* 2015; 11: 962-972. 2013/08/15. DOI: 10.1111/mcn.12076.
18. Laillou A, Prak S, de Groot R, et al. Optimal screening of children with acute malnutrition requires a change in current WHO guidelines as MUAC and WHZ identify different patient groups. *PLoS One* 2014; 9: e101159. 2014/07/02. DOI: 10.1371/journal.pone.0101159.
19. WHO. Guideline: updates on the management of severe acute malnutrition in infants and children. Geneva: World Health Organisation, 2013.
20. Mogendi JB, De Steur H, Gellynck X, et al. Efficacy of mid-upper arm circumference in identification, follow-up and discharge of malnourished children during nutrition rehabilitation. *Nutr Res Pract* 2015; 9: 268-277. 2015/06/11. DOI: 10.4162/nrp.2015.9.3.268.
21. Tadesse AW, Tadesse E, Berhane Y, et al. Comparison of Mid-Upper Arm Circumference and Weight-for-Height to Diagnose Severe Acute Malnutrition: A Study in Southern Ethiopia. *Nutrients* 2017; 9 2017/03/14. DOI: 10.3390/nu9030267.
22. Hall G, Chowdhury S and Bloem M. Use of mid-upper-arm circumference Z scores in nutritional assessment. *Lancet* 1993; 341: 1481. Letter.
23. Roberfroid D, Huybregts L, Lachat C, et al. Inconsistent diagnosis of acute malnutrition by weight-for-height and mid-upper arm circumference: contributors in 16 cross-sectional surveys from South Sudan, the Philippines, Chad, and Bangladesh. *Nutr J* 2015; 14: 86. 2015/08/26. DOI: 10.1186/s12937-015-0074-4.