Lipid accumulation product (LAP) index as a potential risk assessment for cardiovascular risk stratification among type II diabetes mellitus in a Ghanaian population: A cross-sectional study

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Abstract: The study determined the comparative usefulness of Lipid Accumulation Product (LAP) index, for identifying individuals at immediate risk of cardiovascular diseases in a Ghanaian population. A cross-sectional study that involved 324 T2DM patients attending the Eastern Regional Hospital, Koforidua, Ghana was selected using a simple random sampling method. Height, body weight, and waist circumference (WC) of all study participants were measured; Body Mass Index (BMI) was derived from the measurements of height and weight. Fasting blood samples were collected for lipids and glucose measurements. Lipid accumulation product index was estimated from waist circumference and plasma triglycerides concentration. Ten-year risk of general CVD morbidity was estimated using the Framingham risk estimation criteria. Mean age of the study participants was 57.2 (±7.2 SD). LAP index (z-scores) was significantly associated and predictive of Metabolic Syndrome (MetS)

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The research activities of our group are focused on cardiovascular risk prevention and early detection. Our major objective is assessing the comparative usefulness of routine markers suitable for screening and detecting patients at risk of cardiovascular morbidity in resource limited clinics. Some research areas we consider include candidate gene studies and its association with disease/outcome, cancer genomics, disease markers and cardiology. Our research team are closely working as affiliates to hospitals and research institutions towards developing management options and strategies for common non-communicable diseases. This research paper addresses an important issue in type-2 diabetes (T2DM) management in a Ghanaian population. The usefulness of LAP as a surrogate marker for cardiovascular risk has not been explored in Ghana, especially in resource limited settings for decision-making in terms of prevention. Thus, this research paper opens the usefulness and applicability of LAP index among T2DM patients in Ghana and evidence for future investigations.

PUBLIC INTEREST STATEMENT
Type-2 diabetes mellitus (T2DM) is responsible for at least 90% of all cases of diabetes mellitus, where it barely occurs without associated conditions of heart and vascular-related problems. Over the years, systematic measurements of size, shape, and composition (especially body mass index and waist circumference) of the human body have been used alongside routine fasting glucose measurement as a marker for individual cardiovascular risk stratification and subsequent decision for primary prevention. LAP represents a useful tool for screening cardiometabolic risk factors and has proven superior over waist circumference and body mass index that is routinely used in Ghana. LAP index emerged as a useful index cardiovascular risk, capable of screening T2DM patients for primary prevention. Being a reliable indicator and a surrogate marker, LAP saves patients the cost of further expensive metabolic profile test and a decision tool for primary preventive strategies.
by IDF [OR = 11.91 (4.76–29.75), p-value <0.0001], MetS by WHO [OR = 2.19 (1.50–3.21), p-value <0.0001], coronary risk index [OR = 2.58 (1.79–3.70), p-value <0.0001], and high probability outcome of 10-year CVD events [OR = 1.97 (1.42–2.74), p-value = 0.001], independent of BMI and WC. The covariate-adjusted area under the curve (AUC) for LAP was excellent in predicting MetS defined by IDF (0.920). The adjusted AUC for LAP proved very good at predicting MetS defined by WHO criteria [0.811] and elevated probability outcome of 10-year CVD events (0.889). Findings from this study suggest that LAP index could be considered as a routine assessment tool in T2DM patients since it is a better predictor than the clustering of BMI and WC.

Subjects: Allied Health; Health Conditions; Medicine; Nursing; Allied Health;

Keywords: Lipid accumulation product index; cardiometabolic risk clustering; metabolic syndrome; type-2 diabetes mellitus; framingham 10-year probability risk of cardiovascular events

1. Introduction

Cardiometabolic risk (CMR) syndrome has widely been defined as a cluster of metabolic abnormalities predictive of diabetes and cardiovascular disease (CVD) (Kirk & Klein, 2009). In practice, there are no universally adopted criteria for defining CMR syndrome, although, major independent organizations have proposed the clinical criteria for establishing CMR syndrome form a constellation of obesity and metabolic abnormalities. The most widely accepted criteria include those proposed by the World Health Organization (WHO) (Organization, 2000), the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) (NCEP-ATP III) (Expert Panel on Detection, 2001), the American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement (Grundy et al., 2005) and the International Diabetic Federation (IDF) (Ford, 2005) which share common components like central obesity, insulin resistance, dyslipidaemia, and increased blood pressure.

The global estimate indicates that there is a surge in CMR syndrome prevalence as high as 20–30% among the adult healthy population, which consequently affects clinical and public health (Ford, Giles, & Mokdad, 2004). In Ghana, a recent study by Osei-Yeboah et al. (2017) reported a prevalence of CMR syndrome among type-2 diabetes mellitus (T2DM) patients to be 43.83%, 63.58%, and 69.14% using the NCEP-ATP III, the WHO, and the IDF criteria, respectively. Other studies have indicated a different prevalence rate of CMR among different subpopulations based on different criteria. In a Ghanaian rural community, Gyakobo, Amoah, Martey-Marbell, and Snow (2012) has also reported a CMR prevalence of 35.9% using the IDF definition. Similar study by Arthur, Adu-Frimpong, Osei-Yeboah, Mensah, and Owusu (2013) has reported a 35.9% prevalence of CMR using the IDF criteria. T2DM remains one of the most common chronic diseases globally and its complications include CVD, retinopathy, nephropathy, and neuropathy among others (Grundy et al., 1999). The mechanism underlying the development of T2DM, that is, multi-organ insulin resistance, is a common feature for CMR syndrome prevalence (Kirk & Klein, 2009). Thus, the incidence of CVD is common with this condition as a result of the increasing evidence of CMR factors. The incidence rate of these clusters of metabolic abnormalities among T2DM is high; reported prevalence range from 24% to 78% among T2DM populations in Ghana (Mogre, Salifu, & Abedandi, 2014; Nsiah, Shang, Boateng, & Mensah, 2015; Titty, 2010). Recently, Obirikorang et al. (2018) reported a 76.3% prevalence of CMR syndrome among T2DM patients in Ghana.

The identification of markers of CMR could provide new information about the pathogenesis and early diagnosis of complications in T2DM and expedite the decision-making in terms of prevention.
and treatment. In recent years, studies have demonstrated the diagnostic applicability of Lipid Accumulation Products (LAP) index, as a reliable biomarker than other anthropometric measurements like BMI, WC, and WHtR for identifying individuals at risk of cardiometabolic outcomes (Angelo Vieira et al., 2015; Macut et al., 2012; Mazidi, Kengne, Katsiki, Mikhailidis, & Banach, 2018). It has been proposed as a novel index of central lipid accumulation that is associated with cardiovascular diseases (Kahn, 2005). LAP defines the magnitude to which an individual has increasing evidence of abdominal obesity and hypertriglyceridaemia. Taverna, Martínez-Larrad, Frechtel, and Serrano-Ríos (2011), have recently indicated that LAP has a strong and reliable diagnostic accuracy for MetS.

In Ghana and most developing countries, economic and resource limitations restrict most diabetic clinics to follow the recommended T2DM management, and prognostic outcomes since most of these follow-up tests require expensive procedures. Thus, patients in such regions are rarely screened for CMR markers except in acute conditions. Hence, establishing markers of cardiometabolic risk is essential in such limited clinics to establish a routine management panel to identify high-risk T2DM patients for primary prevention. The study proposed Lipid accumulation products (LAP) index, as a reliable biomarker for identifying individuals at immediate risk of CVD outcomes than the conventional BMI and WC at Eastern Regional Hospital, Koforidua (ERHK) for individual risk stratification. This study, therefore, investigated the predictive and discriminatory ability of LAP to identify individuals at risk of cardiometabolic abnormalities among adult T2DM at the ERHK.

2. Materials and methods

2.1. Study design/site
The study was conducted at the Eastern Regional Hospital, Koforidua (ERHK), situated in the capital city (Koforidua) in the Eastern region of Ghana, in the New Juaben Municipality. Participants were recruited by simple random sampling at the diabetic clinic for this cross-sectional study from April 2018 to September 2018.

2.2. Participant selection criteria
Participants for this study were recruited from among T2DM patients aged 35–70 years who had no infection or any other chronic disease at the time of the study. Individuals whose medical records indicated probable alteration of metabolic profile arising from conditions including peripheral vascular disease (PVD), inflammatory, and autoimmune disorders such as rheumatoid arthritis (RA), and other indications of corticosteroid therapy were excluded from this study.

2.3. Sample size determination
Using a proportionate rate of 20.5%, a confidence level of 95% (z-score 1.96), and margin of error of 5%, the minimum size required was 246 using the formulae adopted from Pourhoseingholi, Vahedi, and Rahimzadeh (2013). However, to accommodate a non-response rate of 20.0% and stronger statistical power and effect size, the samples were projected to 324 participants.

3. Data collection

3.1. Questionnaire interview
A pretested-designed questionnaire was used to assess demographic data (including age, duration of the condition, and gender) participants, medical, and medication history from patients folders. Medication adherence data were obtained using the Morisky 8-item questionnaire (Al-Qazaz et al., 2010). Patients with complete data without any chronic condition reviewed from folder were included.

3.2. Anthropometric measurements
An automated sphygmomanometer (Omron M7 Intelli IT) was used for the measurements of blood pressure. Three consecutive readings of blood pressure measurements were taken from the patients’ right arm and the mean of two closest value was recorded.
Body weight of all participants expressed in 0.1-Kg intervals was taken at fasting state using an automated weighing scale. Portable height rod stadiometers were used for height measurements to the nearest centimetre. BMI was calculated as the ratio of body weight to height (Kg/m²). Waist circumference at the midpoint between the anterior superior iliac crest and the lowest rib was measured in centimetres using a tape measure.

3.3. Biochemical analysis

Six millilitres (6 ml) of the venous blood sample was taken from each participant following an 8–12 h overnight fast, for biochemical analyses. Four millilitres (4 ml) of the sample was placed in a serum separator tube and 2 ml in a Sodium Fluoride tube for serum lipids; high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), Triglycerides (TGs), Total cholesterol (TC), and plasma glucose measurements, respectively, using SELECTRA-PRO M chemistry analyser (EliTechGroup B.V, Netherlands).

3.4. Definition of clinical characteristics

Cluster of cardiometabolic abnormalities was defined in two parts: (a) a constellation of at least three of the following indications—overweight or obesity (BMI >25.0 Kg/m²), Isolated or systolic/diastolic hypertension (SBP >140 mmHg, DBP >90 mmHg), atherogenic dyslipidaemia (defined as the presence of any two of Low HDL-C (<1.03 mmol/L in males and <1.29 mmol/L in females), elevated LDL-C > 3.37 mmol/L, and elevated triglycerides >1.7 mmol/L) and uncontrolled fasting sugar (>6.9 mmol/L); (b) a constellation of all of the following indications—overweight or obesity (BMI >25.0 Kg/m²), Isolated or systolic/diastolic hypertension (SBP >140 mmHg and DBP >90 mmHg), atherogenic dyslipidaemia (defined as the presence of any two of Low HDL-C (<1.03 mmol/L in males and <1.29 mmol/L in females), high LDL-C > 3.37 mmol/L, elevated triglycerides >1.7 mmol/L) and uncontrolled fasting sugar (>6.9 mmol/L). LAP was calculated as \[WC - 65 \times [TG (mmol/L)]\] in men, and \[WC - 58 \times [TG (mmol/L)]\] in women (Mirmiran, Bahadoran, & Azizi, 2014).

Probability risk of 10-years general CVD morbidity was estimated using the procedure described by D’agostino et al. (2008) and categorized as high risk (≥20%) and low-moderate risk (<20%). MetS was defined using the International Diabetes Federation and the World Health Organization’s criteria (Parikh & Mohan, 2012).

3.5. Statistical analysis

All statistical analyses were performed using IBM Statistical Package for Social Sciences (SPSS), version 22. Mean and Standard deviations were used to summarize continuous variables; categorical data were presented as frequency (%). Skewed continuous variables were presented as median (interquartile range). T-test, Mann–Whitney test, and Chi-square test were used to compare continuous, skewed, and categorical data, respectively. Univariate-adjusted and multivariable logistic regression analysis was used to study the association and predictability of putative markers for clustered cardiometabolic abnormalities and CVD morbidity. Selected covariates and factors used for the stepwise backward (P remove: 0.1) multivariate regression model included age and duration of condition (for clustered of cardiometabolic risk-a); medication adherence and duration of condition (for clustered of cardiometabolic risk-b), age, gender, and medication adherence (for MetS defined according to IDF); age, gender, and duration of condition (for MetS defined by WHO); age, gender, and duration of condition (for risk of 10-year CVD morbidity). LAP was entered into the model as both standardized (z-scores) and unstandardized. Receiver operative characteristics (ROC) curves were used to demonstrate the discriminatory ability of each model generated over the entire range of possible values in the detection of a cardiometabolic outcome as measured by the area under the curve (AUC). The ideal cut-off point for each model variables in the prediction of a cardiometabolic outcome was established based on the highest combination of sensitivity and specificity. Measurement of diagnostic accuracy of LAP was demonstrated using diagnostic odds ratios, corrected group classifications and Cohen's kappa analysis. P-values of less than 0.05 were considered statistically significant.
4. Results

Demographic and cardiometabolic profile of the study participants is summarized in Table 1. Duration of condition was significantly higher among T2DM women than male participants [4.0 (3.0–8.0) vs 3.0 (2.0–5.0), p-value = 0.027]. Mean WC was significantly higher among women than men (102.01 ± 13.47 vs 93.27 ± 13.8, p-value <0.0001). Similarly, BMI and LAP estimates were significantly higher among T2DM women than men (p-value <0.01). Fasting plasma glucose (11.91 vs 9.67, p-value = 0.007) and SBP (137.96 vs 132.63, p-value = 0.046) measurements were found to be significantly higher among male T2DM subjects than females, respectively. Moreover, mean TC (5.23 vs 4.88) and TG (2.54 vs 2.15) measurements were significantly higher among female T2DM participants than male counterparts, respectively (p-value <0.05). Prevalence of systolic/diastolic hypertension, isolated systolic, and diastolic hypertension were, respectively, 15.7%, 21.3%, and 7.4%, which was presented on equivalent proportions among T2DM male and female subjects. Higher triglycerides and TC levels were present among 75% and 51.9% of the study participants and were observed among a significantly higher proportion of female participants than male (p-value <0.05). The mean probability risk of 10-year CVD events was higher in males than females (32.06 ± 15.34 vs 19.48 ± 10.83, p-value <0.0001). MetS defined by the IDF criteria was prevalent among 83.3% of the study participants, which was significantly common (p-value <0.0001) among female participants (87.8%) than male subjects (69.2%). Similarly, MetS defined by WHO criteria was prevalent in a higher proportion among female participants (51.2%) than male participants (26.9%) (p-value <0.0001). Cluster of CMR factors (a, b) was prevalent in equivalent proportions among male and female participants (p-value >0.05).

Table 2 shows the association and predictiveness of BMI, WC, and LAP indices to cardiometabolic risk factors among T2DM participants. In the univariate-adjusted model, for every 1 unit increase in LAP (unstandardized), there was corresponding likelihood increase in MetS-IDF (beta = 0.05), MetS-WHO (beta = 0.02), cluster of CMR factors (beta = 0.01), coronary risk (beta = 0.01), and elevated 10-year risk of general CVD (beta = 0.01). The odds per standard deviation increase in LAP increase the likelihood prevalence of MetS defined by IDF [OR = 15.02 (6.08–37.11), p-value <0.0001], MetS defined by WHO (OR = 3.57 (2.55–4.98), p-value <0.0001), cluster of multiple cardiometabolic abnormalities [OR = 1.50 (1.18–1.91), p-value = 0.001], coronary risk [OR = 1.74 (1.33–2.27), p-value = 0.0001], and elevated 10-year probability risk of CVD morbidity [OR = 1.97 (1.42–2.74), p-value = 0.0001]. In the multivariate-adjusted model, the odds per standard deviation (SD) increase in LAP were found to be independent of other obesity markers (WC and BMI) in predicting the elevated risk of 10-year CVD morbidity by 97.0% (95% CI: 45% to 174%, p-value = 0.001). Similarly, for every one SD increase in LAP, there was an associated 11.91, 2.19, and 2.58 likely prevalence of MetS (IDF criteria), MetS (WHO criteria), and coronary risk independent of BMI and WC. The covariate-adjusted AUC for LAP was excellent in predicting MetS defined by IDF [0.920 (95% CI: 0.885–0.947)]. Similarly, the adjusted AUC for LAP proved very good at predicting MetS defined by WHO [0.811 (95% CI: 0.764–0.853)] and elevated 10-year risk of CVD events [0.889 (0.850–0.921)]. Also, in the adjusted AUC for LAP, it proved sufficient in predicting cluster of multiple cardiometabolic risk factors (0.668) and coronary risk (0.672).

Table 3 shows the comparison of CMR factors and probability risk of CVD morbidity by LAP tertiles. Compared to the lower tertiles of LAP, the higher tertiles (T2 and T3) tend to have higher mean TC/HDL-C ratios, and 10-year probability risk of general CVD morbidity (p-value <0.05). Also, except for the cluster of cardiometabolic risk (b), the prevalence of MetS (defined by IDF or WHO), dyslipidaemia, cluster of at least three cardiometabolic abnormalities (b), coronary risk, high risk of 10 years general CVD morbidity increases with the tertiles of LAP (T1 < T2 < T3) respectively.

Table 4 shows the discriminatory ability of LAP in identifying individuals at immediate CDV risk. A LAP cut-off value of 66.0 (z-score equivalent = −0.59) correctly classified 83.3% of the participants with diagnostic odds ratio of 17.30. Similarly, various LAP cut-off values or its z-score equivalent, for predicting MetS (WHO), clustered of cardiometabolic risk factors (a and b), coronary risk, and 10-year risk of CVD correctly classified 54.6%, 62.0%, 88.9%, 77.8%, and 63.0% of the
Table 1. Demographic and cardiometabolic profile of the study participants by gender

| Variables                               | Women (n = 246) | Men (n = 78) | Total (n = 324) | p-Value |
|-----------------------------------------|-----------------|--------------|-----------------|---------|
| Age (years)T                            | 56.60 ± 7.01    | 58.27 ± 7.77 | 57.0 ± 7.22     | 0.093   |
| Duration of condition T                 | 4.0 (3.0–8.0)   | 3.0 (2.0–5.0)| 4.0 (3.0–8.0)   | 0.027   |
| Medication adherence (Morisky scale) T  | 6.87 ± 1.52     | 6.42 ± 1.94  | 6.76 ± 1.64     | 0.068   |
| Waist circumference (cm) T              | 102.01 ± 13.47  | 93.27 ± 13.38| 99.91 ± 13.94   | <0.0001 |
| Body mass index (Kgm ^{-2}) T          | 29.47 ± 6.20    | 24.90 ± 4.17 | 28.37 ± 6.09    | <0.0001 |
| Lipid Accumulation Product*             | 101.1 (68.3–154.0) | 52.9 (42.2–89.1) | 89.1 (55.7–130.2) | <0.0001 |
| Lipid Accumulation Product (Z-score)    | 0.21 ± 1.00     | -0.67 ± 0.64 | 0.00 ± 1.00     | <0.0001 |
| Diastolic blood pressure (mmHg)         | 83.73 ± 14.47   | 83.65 ± 11.27| 83.71 ± 13.75   | 0.961   |
| Systolic blood pressure (mmHg)          | 132.63 ± 18.87  | 137.96 ± 20.71| 133.92 ± 19.45  | 0.046   |
| HDL-C (mmol/L)                          | 1.24 ± 0.29     | 1.25 ± 0.33  | 1.24 ± 0.30     | 0.897   |
| LDL-C (mmol/L)                          | 2.82 ± 1.00     | 2.63 ± 1.14  | 2.78 ± 1.04     | 0.182   |
| Triglycerides ^ (mmol/L)                | 2.54 ± 0.93     | 2.15 ± 0.98  | 2.45 ± 0.95     | 0.002   |
| Total cholesterol (mmol/L)              | 5.23 ± 1.14     | 4.85 ± 1.31  | 5.13 ± 1.20     | 0.027   |
| TC/HDL-C                                | 4.38 ± 1.28     | 4.05 ± 1.23  | 4.30 ± 1.28     | 0.044   |
| Fasting blood sugar (mmol/L)            | 9.67 ± 4.04     | 11.91 ± 6.85 | 10.21 ± 5.00    | 0.007   |
| 10-year probability risk of general CVD | 19.48 ± 10.83   | 32.06 ± 15.34| 22.51 ± 13.20   | <0.0001 |
| Systolic/diastolic hypertension ^        | 42 (17.1)       | 9 (11.5)     | 51 (15.7)       | 0.287   |
| Isolated systolic hypertension ^         | 51 (20.7)       | 18 (23.1)    | 69 (21.3)       | 0.638   |
| Isolated diastolic hypertension ^        | 15 (6.1)        | 9 (11.5)     | 24 (7.6)        | 0.135   |
| Low HDL ^                                | 42 (17.1)       | 15 (19.2)    | 57 (17.6)       | 0.733   |
| High LDL ^                               | 78 (31.7)       | 24 (30.8)    | 102 (31.5)      | 1.000   |
| High triglycerides ^                    | 198 (80.5)      | 45 (57.7)    | 243 (75.0)      | <0.0001 |
| Variables | T2DM patients | P-Value |
|-----------|---------------|---------|
|           | Women (n = 246) | Men (n = 78) | Total (n = 324) |
| High total cholesterol | 138 (56.1) | 30 (38.5) | 168 (51.9) | 0.009 |
| Dyslipidaemia | 93 (37.8) | 27 (34.6) | 120 (37.0) | 0.687 |
| Coronary risk | 54 (22.0) | 18 (23.1) | 72 (22.2) | 0.835 |
| Uncontrolled FBG (≥7.0 mmol/L) | 162 (65.9) | 60 (76.9) | 222 (68.5) | 0.007 |
| Metabolic syndrome (IDF) | 276 (87.8) | 94 (69.2) | 370 (83.3) | <0.0001 |
| Metabolic syndrome (WHO) | 126 (51.2) | 21 (26.9) | 147 (45.4) | <0.0001 |
| Cluster of cardiometabolic abnormalities (a) | 99 (40.2) | 24 (30.8) | 123 (38.0) | 0.143 |
| Cluster of cardiometabolic abnormalities (b) | 27 (11.0) | 9 (11.5) | 36 (11.1) | 0.39 |
| High risk of 10 years general CVD | 114 (46.3) | 60 (76.9) | 174 (53.7) | <0.0001 |

Variables denoted with ‘T’ are presented as mean ± SD and compared using t-test. Variables with ‘^’ are presented as frequency (within gender proportions) and compared using test of two proportions; ‘*’ represent variables presented as median (interquartile range and compared using Wisconsin’s sign rank test).
## Table 2. Association and predictive of anthropometric indices for cardiometabolic risk factors among T2DM patients

| Variable                        | Univariate adjusted model | Multivariate model | αAUC (95% CI) |
|---------------------------------|---------------------------|--------------------|---------------|
|                                 | B(SE)                     | R²                 | aOR(95% CI)   | P-value | aOR(95% CI) | P-value |
| **MetS (IDF)**                  |                           |                    |               |          |             |         |
| WC                              | 0.09 (0.015)              | 0.426              | 1.09 (1.06-1.12) | <0.0001 | NC          | -       |
| BMI                             | 0.22 (0.045)              | 0.415              | 1.24 (1.14-1.36) | <0.0001 | NC          | 0.014   |
| LAP                             | 0.05 (0.008)              | 0.547              | 1.05 (1.03-1.06) | <0.0001 | 1.04 (1.03-1.06) | <0.0001 |
| LAP z-scores                    | 2.71 (0.461)              | 0.547              | 15.02 (6.08-37.11) | <0.0001 | 11.91 (4.76-29.75) | <0.0001 |
| **MetS (WHO)**                  |                           |                    |               |          |             |         |
| WC                              | 0.10 (0.013)              | 0.385              | 1.10 (1.07-1.13) | <0.0001 | NC          | 0.001   |
| BMI                             | 0.25 (0.034)              | 0.399              | 1.28 (1.20-1.37) | <0.0001 | 1.21 (1.12-1.30) | <0.0001 |
| LAP                             | 0.02 (0.003)              | 0.358              | 1.02 (1.01-1.02) | <0.0001 | 1.01 (1.00-1.02) | <0.0001 |
| LAP z-scores                    | 1.27 (0.171)              | 0.354              | 3.57 (2.55-4.98) | <0.0001 | 2.19 (1.50-3.21) | <0.0001 |
| **Clustered of cardiometabolic abnormalities (a)** |                           |                    |               |          |             |         |
| WC                              | 0.03 (0.009)              | 0.104              | 1.03 (1.02-1.05) | 0.0003  | 1.03 (1.03-1.05) | 0.002   |
| BMI                             | 0.06 (0.020)              | 0.086              | 1.06 (1.02-1.11) | 0.0002  | NC          | -       |
| LAP                             | 0.01 (0.002)              | 0.092              | 1.01 (1.00-1.01) | 0.001   | NC          | -       |
| LAP z-scores                    | 0.41 (0.123)              | 0.092              | 1.50 (1.18-1.91) | 0.001   | NC          | -       |
| **Clustered of cardiometabolic abnormalities (b)** |                           |                    |               |          |             |         |
| WC                              | 0.02 (0.013)              | 0.110              | 1.02 (0.99-1.05) | 0.164   | NC          | -       |
| BMI                             | 0.02 (0.028)              | 0.102              | 1.02 (0.97-1.08) | 0.435   | NC          | -       |
| LAP                             | 0.01 (0.003)              | 0.121              | 1.01 (1.00-1.01) | 0.047   | NC          | -       |
| LAP z-scores                    | 0.34 (0.173)              | 0.121              | 1.41 (1.00-1.98) | 0.047   | NC          | -       |
| **Elevated TC/HDL-C (Coronary risk)** |                           |                    |               |          |             |         |
| WC                              | 0.02 (0.010)              | 0.056              | 1.02 (1.00-1.04) | 0.073   | NC          | -       |
| BMI                             | 0.004 (0.023)             | 0.041              | 1.00 (0.96-1.05) | 0.866   | NC          | -       |
| LAP                             | 0.01(0.002)               | 0.119              | 1.01 (1.00-1.01) | 0.0001  | 1.02 (1.01-1.02) | <0.0001 |

(Continued)
| Variable | Univariate adjusted model | Multivariate model | aAUC (95% CI) |
|----------|---------------------------|--------------------|---------------|
|          | B(SE)                     | R²                 | aOR(95% CI)   | P-value | aOR(95% CI) | P-value |               |
| LAP z-scores | 0.55 (0.137) | 0.119 | 1.74 (1.33-2.27) | 0.0001 | 2.58 (1.79-3.70) | <0.0001 | 0.672 (0.618-0.724) |

High risk of 10-year cardiovascular events

| Variable | Univariate adjusted model | Multivariate model | aAUC (95% CI) |
|----------|---------------------------|--------------------|---------------|
|          | B(SE)                     | R²                 | aOR(95% CI)   | P-value | aOR(95% CI) | P-value |               |
| WC       | 0.04 (0.012)              | 0.535              | 1.04 (1.02-1.06) | 0.001  | NC          | -       | 0.882 (0.841-0.915) |
| BMI      | 0.07 (0.025)              | 0.531              | 1.08 (1.03-1.13) | 0.003  | NC          | -       | 0.880 (0.840-0.914) |
| LAP      | 0.01 (0.003)              | 0.552              | 1.01 (1.00-1.02) | 0.0001 | 1.01 (1.00-1.02) | 0.001  | 0.889 (0.850-0.921) |
| LAP z-scores | 0.68 (0.168) | 0.552 | 1.97 (1.42-2.74) | 0.0001 | 1.97 (1.42-2.74) | 0.001  | 0.889 (0.850-0.921) |

WC - waist circumference; aAUC - adjusted area under the curve; B - beta estimates; aOR - adjusted odds ratio; MetS - metabolic syndrome; CVD - cardiovascular disease; BMI - body mass index; LAP - lipid accumulation products; * the accuracy of the model is not independent of age and gender. Estimated AUC’s were adjusted for individual covariates. NC - not computed.
## Table 3. Comparison of cardiometabolic and risk of CVD morbidity by LAP Tertiles

| LAP (unstandardized) | T1 (<67.26) (n = 105) | T2 (67.26–119.5) (n = 111) | T3 (>119.5) (n = 108) | p-Value |
|----------------------|------------------------|-----------------------------|------------------------|---------|
| TC/HDL-C T1          | 3.73 ± 1.13<sup>a</sup> | 4.37 ± 1.40<sup>b</sup>    | 4.80 ± 1.07<sup>c</sup> | <0.0001 |
| 10-year probability risk of general CVD<sup>+</sup> | 14.05 (9.20–29.87)<sup>a</sup> | 23.76 (10.58–29.75)<sup>b</sup> | 22.80 (12.41–32.49)<sup>c</sup> | 0.048   |
| Dyslipidaemia<sup>+</sup> | 42 (40.0)<sup>a</sup> | 81 (73.0)<sup>b</sup>    | 75 (69.4)<sup>c</sup>    | <0.0001 |
| Coronary risk<sup>+</sup> | 9 (8.6)<sup>a</sup> | 24 (21.6)<sup>b</sup>    | 39 (36.1)<sup>c</sup>    | <0.0001 |
| Metabolic syndrome (IDF)<sup>+</sup> | 60 (57.1)<sup>a</sup> | 105 (94.6)<sup>b</sup>   | 105 (97.2)<sup>b</sup>   | <0.0001 |
| Metabolic syndrome (WHO)<sup>+</sup> | 12 (11.4)<sup>a</sup> | 63 (56.8)<sup>b</sup>    | 72 (66.7)<sup>b</sup>    | <0.0001 |
| Cluster of CMRF (a)<sup>+</sup> | 24 (22.9)<sup>a</sup> | 48 (43.2)<sup>b</sup>    | 51 (47.2)<sup>b</sup>    | <0.0001 |
| Cluster of CMRF (b)<sup>+</sup> | 9 (8.6)<sup>a</sup> | 8 (8.1)<sup>a</sup>    | 18 (16.7)<sup>a</sup>    | 0.079   |
| High risk of 10 years general CVD<sup>+</sup> | 42 (40.0)<sup>a</sup> | 69 (62.2)<sup>b</sup>    | 63 (58.3)<sup>b</sup>    | 0.002   |

| LAP (Z-score) | T1 (<-0.570) (n = 105) | T2 (~0.570–0.32) (n = 114) | T3 (>0.32) (n = 105) | p-Value |
|---------------|------------------------|-----------------------------|------------------------|---------|
| TC/HDL-C T1   | 3.73 ± 1.13<sup>a</sup> | 4.37 ± 1.38<sup>b</sup>    | 4.80 ± 1.07<sup>c</sup> | <0.0001 |
| 10-year probability risk of general CVD<sup>+</sup> | 14.05 (9.20–29.87)<sup>a</sup> | 23.79 (10.58–30.53) | 22.07 (12.31–32.84) | 0.058   |
| Dyslipidaemia<sup>+</sup> | 42 (40.0)<sup>a</sup> | 84 (73.7)<sup>b</sup>    | 72 (68.6)<sup>b</sup>    | <0.0001 |
| Coronary risk<sup>+</sup> | 9 (8.6)<sup>a</sup> | 24 (21.1)<sup>b</sup>    | 39 (37.1)<sup>c</sup>    | <0.0001 |
| Metabolic syndrome (IDF)<sup>+</sup> | 60 (57.1)<sup>a</sup> | 108 (94.7)<sup>b</sup>   | 102 (97.1)<sup>b</sup>   | <0.0001 |
| Metabolic syndrome (WHO)<sup>+</sup> | 12 (11.4)<sup>a</sup> | 63 (55.3)<sup>b</sup>    | 72 (68.6)<sup>b</sup>    | <0.0001 |
| Cluster of CMRF (a)<sup>+</sup> | 24 (22.9)<sup>a</sup> | 51 (46.7)<sup>b</sup>    | 48 (45.7)<sup>b</sup>    | 0.001   |
| Cluster of CMRF (b)<sup>+</sup> | 9 (8.6) | 9 (7.9)    | 18 (17.1)    | 0.056   |
| High risk of 10 years general CVD<sup>+</sup> | 42 (40.0)<sup>a</sup> | 72 (63.2) | 60 (57.1) | 0.002   |

T1-tertile one; T2-tertile two; T3-tertile three; CMRF-cardiometabolic risk factors; CVD-cardiovascular disease. Variables denoted with T are presented as mean ± SD and compared using one way analysis of variance. Variables with ^ are presented as frequency (within tertiles proportions) and compared using test of k proportions; * represent variables presented as median (interquartile range and compared using Kruskal Wallis test). All post-hoc analysis were corrected for Bonferroni factor, "b and c superscript" are significantly different from "a superscript".
Table 4. Discriminatory ability of LAP to identify individuals at immediate CVD risk

| Discriminators                      | Sensitivity (%) | Specificity (%) | Diagnostic odds ratio | Cut-off  | Corrected group classification (%) | Cohen's Kappa |
|-------------------------------------|-----------------|-----------------|-----------------------|----------|-------------------------------------|---------------|
| LAP (unstandardized)                |                 |                 |                       |          |                                     |               |
| MetS (IDF)                          | 77.78           | 83.33           | 17.30                 | >66.0    | 83.3                                | 0.444         |
| MetS (WHO)                          | 83.67           | 67.80           | 10.83                 | >74.9    | 54.6                                | 0.505         |
| Clustered of CMRF (a)               | 73.17           | 49.25           | 2.64                  | >72.93   | 62.0                                | 0.202         |
| Clustered of CMRF (b)               | 75.00           | 61.46           | 4.78                  | >96.96   | 88.9                                | 0.156         |
| Coronary risk                       | 62.50           | 72.76           | 4.17                  | >113.1   | 77.8                                | 0.277         |
| 10-year risk of CVD’s               | 70.69           | 54.00           | 2.83                  | >72.93   | 63.0                                | 0.249         |
| LAP (z-scores)                      |                 |                 |                       |          |                                     |               |
| MetS (IDF)                          | 77.78           | 83.33           | 17.30                 | >-0.59   | 83.3                                | 0.444         |
| MetS (WHO)                          | 83.67           | 67.80           | 10.83                 | >-0.44   | 54.6                                | 0.505         |
| Clustered of CMRF (a)               | 53.66           | 68.66           | 2.54                  | >0.04    | 62.0                                | 0.202         |
| Clustered of CMRF (b)               | 75.00           | 61.46           | 4.78                  | >-0.02   | 88.9                                | 0.156         |
| Coronary risk                       | 62.50           | 72.76           | 4.17                  | >0.21    | 77.8                                | 0.277         |
| 10-year risk of CVD’s               | 70.69           | 54.00           | 2.83                  | >-0.48   | 63.0                                | 0.249         |

CMRF-cardiometabolic risk factors
study participants. The consistency in risk estimation using the various cut-off values ranged from minimal (kappa = 0.156) to weak (kappa = 0.505).

5. Discussion
Cardiometabolic risk (CMR) denotes a cluster of metabolic abnormalities predictive of cardiovascular diseases (CVD), which is 3–4 times identifiable among individuals with Type-2 Diabetes Mellitus (T2DM) (Kirk & Klein, 2009). Thus, it is essential to use reliable markers that readily identify patients at risk of CVDs for timely intervention. This study investigated the comparative usefulness of Lipid Accumulation Product (LAP) in identifying individuals at immediate risk of CVDs in a Ghanaian population.

This study demonstrates that cardiometabolic risk factors are prevalent among individuals with T2DM. Obesity or overweight was higher as demonstrated by the higher mean BMI and WC levels among the study subjects. This observed feature adds to the evidence of existing knowledge that obesity epidemic parallels T2DM prevalence as an underlying pathology or a risk factor for disease prevalence. A recent study has indicated that while the role of the renin-angiotensin-system (RAS) is essential among patients with high blood pressure, it has an alternative role involved in energy balance and metabolism thus, suggesting its influences in weight gain (Cabandugama, Gardner, & Sowers, 2017). In this present study, the majority of the study subjects had elevated blood pressure which could partly align with the above-stated observation. It is also known that when peripheral renin-angiotensin system (RAS) activity is increased, resting metabolism is suppressed by angiotensin (AT)-2 receptor, causing weight gain (Littlejohn et al., 2016). Also, among T2DM patients, in addition to the many conventional glucose-lowering agents associated with weight gain (Group, 1998; Van Gaal & Scheen, 2015), metabolic, psychological, and behavioural factors also influence weight gain among T2DM patients (Cabrera et al., 2012; Toft et al., 2006). Again, the homeostatic control of body weight is also regulated by a complex neurohormonal system that involves a feedback loop between the brain and peripheral tissues, and perturbations to this system (which is common among hypertensives and T2DM patients) affect weight status (MacLean, Bergouignan, Cornier, & Jackman, 2011).

Due to the constellation of metabolic abnormalities frequently seen among the vulnerable population like T2DM patients, there is the need to elucidate a marker that can best identify high-risk individuals for immediate intervention. LAP is a modest indicator that involves the determination of circulating TG and measurement of WC. This present study shows that LAP index is a more reliable tool than BMI and WC in the prediction of cardiometabolic risk among T2DM patients. Higher LAP measurements were associated with the increased likelihood of one or more cardiometabolic risk prevalence and probability risk of cardiovascular morbidity among T2DM population. In previous studies, LAP has been reported as a predictive biomarker for MetS and CVD prevalence better than BMI (Kahn, 2005; Xiang et al., 2013). In a study by Ioachimescu, Brennan, Hoar, and Hoogwerf (2010), the authors indicated that LAP may represent a useful tool in clinical practice to stratify the possibility of adverse outcome related with obesity. Mazidi et al. (2018), suggested that LAP index is a simple, cheap, and accurate surrogate marker of homeostatic model assessment (HOMA)-diagnosed insulin resistance. However, Mazidi et al. mentioned that LAP index is not perfect owing to its lower specificity in predicting insulin resistance compared with anthropometrically predicted visceral adipose tissue (apVAT). The potential of LAP in the prediction of metabolic profile in hospitalized patients (Angelo Vieira et al., 2015), higher insulin resistance, oxidative stress and systemic inflammation among T2DM patients (Mirmiran et al., 2014), and MetS among women with polycystic ovarian syndrome (Macut et al., 2012) has also been established. LAP index was observed to be higher in women compared with men. This may be explained by the fact that the indices for LAP estimation; WC, which is an index for intra-abdominal adipose tissue and TG, which is a proxy measure of unused calories in the human body were observed to higher among
women compared with men. This observation is similar to the findings of Wang et al. (2018) who observed higher LAP estimates among females compared with males.

Although WC and BMI require only a single anthropometric measurement of waist, weight, and height, the use of LAP as a predictor proved to be more beneficial. In recent studies, visceral adipose tissue has been shown to possess a higher rate of lipolysis, and higher production of adipocytokines, such as interleukin-6 and plasminogen activator inhibitor-1 which is more correlated to cardiometabolic risks compared with subcutaneous adipose tissue (Freedland, 2004; Hamdy, Porramatikul, & Al-Ozaire, 2006). Despite the frequent use of BMI, Shuster, Patlas, Pinthus, and Mourtzakis (2012) indicated that it lacks the ability to distinguish between lean and fat body mass and hence does not identify differences between subcutaneous and visceral fat compartments. Also, WC has the limitation of distinguishing between visceral adipose tissue and subcutaneous adipose tissue as demonstrated in a study by Chiang and Koo (2012).

The strength and comparative advantage of LAP in the prediction of cardiometabolic abnormalities among T2DM adult population is that the primary quantitative lipid abnormalities – hypertriglyceridaemia and low HDL-C levels – are already established promoters of atherosclerosis (Verges, 2005). This phenomenon stems from augmented insulin activity arising from insulin resistance states, which causes increased circulating free fatty acids and accumulation of triglycerides and fatty acid-derived metabolites in muscle and liver (Saltiel & Kahn, 2001). TG has been described to have a significant correlation to visceral adipose tissue, even after controlling for the effect of abdominal subcutaneous adipose tissue (Nguyen-Duy, Nichaman, Church, Blair, & Ross, 2003). Also, indices of triglycerides such as hypertriglyceridaemic waist have the evidence of discriminating individuals with the greatest amount of visceral fat with consequent immediate cardiovascular risk (Blackburn et al., 2012; Sam et al., 2009; Zainuddin, Isa, Muda, & Mohamed, 2011). This study and other related investigations indicate that by combining the discriminatory ability of both WC and TGs, LAP proves to be a reliable indicator for the evaluation of visceral adiposity (Chiang & Koo, 2012; Sam et al., 2009), cardiometabolic risk factors and 10-year probability risk of general CVD incidence.

Notwithstanding the importance of this novel study conducted among adult T2DM Ghanaians, the findings are inherently limited by the cross-sectional design. Further, the generally predominant health-seeking behaviour of women in Ghana compared to men rendered a bias in sampling. Some statistical applications also proved redundant, therefore gender specific discriminatory ability of LAP was not investigated.

6. Conclusion

The study identified that cardiometabolic risk factors are common with T2DM patients. Obesity cluster with at least two metabolic abnormalities: dyslipidaemia, high blood pressure, and hyperglycaemia among T2DM patients. LAP is a useful biomarker for elucidating individuals at immediate risk of cardiovascular outcomes among T2DM patients. LAP may, therefore, be considered a routine assessment tool for T2DM for risk assessment among affected individuals seeking medical attention in health facilities in Ghana.

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