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APOA1 AND APOA2 proteins as prognostic markers for early detection of urinary bladder cancer

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ABSTRACT

Studying the urine proteome is one of the most promising diagnostic biomarkers for urinary bladder cancer patients. The aim of the present study is to assess blood and urinary protein expression levels of Apo-A1 and Apo-A2 in bladder cancer patients. The expression of Apo-A1 and Apo-A2 levels with tumor stage and grade was also assessed. The study was conducted on 50 patients with carcinoma of urinary bladder, 50 patients with cystitis and 50 normal healthy subjects. Protein expression levels of Apo-A1 and Apo-A2 were assessed by western blot technique. Results showed that levels of Apo-A1 and Apo-A2 in voided urine were significantly elevated in the malignant group in comparison to benign and healthy control groups. Apo-A1 and Apo-A2 showed sensitivity and specificity of 100%. Urinary levels of Apo-A1 and Apo-A2 are not correlated to their corresponding blood levels which showed no significant difference between the malignant group and the control group. There was no significant correlation between Apo-A1 and Apo-A2 levels with any of the clinical or pathological data of the disease. Conclusion: The present study demonstrated that ApoA1 and ApoA2 urinary protein levels could be used as a non-invasive highly sensitive diagnostic and screening biomarker for bladder cancer.

1. Introduction

Bladder cancer became a common cancer ranks as the ninth major frequently-diagnosed malignancy globally (Mahdavifar et al., 2016). For the vast majority frequency rates observed in men is found in Western Europe, North America, likewise on specific countries in Northern Africa or Western Asia (Khattab et al., 2015). The highest incidence rate of bladder cancer is recorded in Egypt (37.1 per 100,000 males) (Hammam et al., 2015). According to National Cancer Institute in Egypt, urinary bladder tumor constitutes 30% of all cancer cases with an incidence rate of 13.5/100,000 individuals (Mohamed et al., 2017). The present standard for identification of bladder tumor depends with respect to cystoscopy, an invasive procedure, furthermore cytology (Ellakwa et al., 2016). Cytology has a high specificity, but low sensitivity in identification of low-grade tumors, as well as requires a well-prepared pathologist for review (Fouad et al., 2019). As a result current diagnostic tools are less than optimal and because bladder cancer has a high rate of recurrence and long term following is a necessity, a better diagnostic device is necessary (Onile et al., 2017). Apolipoprotein A-1 (Apo-A1) is the major protein part of high-density lipoprotein (HDL). It is synthesized mostly in the liver and small digestive tract. Likewise affirmed by several studies, Apo-A1 suppresses inflammation, tumor growth, angiogenesis, invasion and metastasis (Mangaraj et al., 2016). Studies have discovered that Apo-A1 is a potential biomarker for numerous types of cancer including breast furthermore pancreatic carcinomas (Cine et al., 2014). It is usually thought that the role of the Apo-A1 molecule over malignancy pathophysiology may be connected with the phospholipid binding ability. Lysophospholipids, in particular, have been demonstrated to play a basic role in the improvement for malignancy and what's more bring been accounted to be major biomarkers for cancerous diseases (Lv et al., 2011). Apolipoprotein A2 (Apo-A2) is the second major protein of the HDL-C particles and comprises about

Abbreviations: Apo-A1, Apolipoprotein A-1; Apo-A2, Apolipoprotein A2; HDL, high density lipoprotein; AUC, Area under the curve; EDTA, ethylenediaminetetraacetic acid; r, correlation coefficient; RIPA, recombinant immunoblot assay; ROC curves, Receiver operating characteristics curves; TBS, tris-buffered saline; μg, micro gram; μl, microliter; μM, micromolar; mM, millimolar; ng, nano gram; OR, odds ratio; p, p. value; PVDF, polyvinylidenedifluoride; SD, standard deviation; SPSS, statistical package for the social sciences

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20% of the total HDL-C protein content. Additionally, Apo-A2 has been related to various types of cancer in different clinical studies (Bandarian et al., 2016). In the present study, blood and urine levels of Apo-A1 and Apo-A2, as were assessed by western blot analysis to measure expression levels of the proteins and genes. The expression of Apo-A1 and Apo-A2 levels with tumor stage and grade was also assessed.

2. Subjects and methods

2.1. Study population

Subjects of the present study were selected from Kasr El-Ainy Hospital, Urology Department Cairo University, Egypt and diagnosed as bladder cancer by histopathological examination of biopsy cystoscopy samples. Laboratory work was conducted in Unit of Biochemistry and Molecular Biology, Faculty of Medicine, Cairo University. The present study was directed as stated by those professional ethics of declaration of Helsinki. Every one of subjects of the present study has signed written informed consents which were affirmed by the Ethics Committee of Cairo University.

Groups of the study: Group I: Involved 50 patients with urinary bladder carcinoma diagnosed by pathological examination of cystoscopy biopsy tissue samples. Group II: Involved 50 patients with cystitis (benign condition). Group III: Involved 50 healthy normal subjects. Inclusion criteria include: age 48–65 years, bladder biopsy showing histological evidence of bladder cancer, patients not receiving any medications, surgery or radiological interventions, no associated chronic diseases or their complications or any other type of tumors. Exclusion criteria include: The presences of any chronic systemic illness were excluded from this study such as patients with chronic kidney, liver, cardiac diseases, hypertension, diabetes mellitus, autoimmune disease, pregnant females, severe obesity or patients receiving any medications.

2.2. Sample collection and processing

Whole blood samples on ethylenediamine tetraacetate (EDTA) were collected and divided into two parts; 3 mL for separation of the mononuclear cell layer by Ficoll Paque (Munich, Germany) and 3 mL for serum separation. Blood and serum samples were stored at −80 °C till the time of laboratory assays.

2. Voided morning urine samples (50–100 ml) were collected from all patient groups before they receive any medications. Urine samples were collected before cystoscopy, surgery or any radiological interventions. Samples were centrifuged at 4000*g* for 20 min. Urine supernatant was stored at −80 °C until used for protein assay.

2.3. Western blot technique was conducted for assessment of Apo-A1 and Apo-A2 protein levels usingV3 Western Workflow™ Complete System, Bio-Rad® Hercules, CA, USA.

Briefly, urine samples and blood samples containing 5 mg proteins were homogenized in recombinant immunoblot assay (RIPA) buffer, then centrifugation at 12,000 rpm for 20 min. The protein concentration for each homogenized sample was determined using Bradford assay. Equal amounts of protein (20–30 µg of total protein) were separated by SDS-PAGE and then transferred to a polyvinylidenedi fluoride (PVDF) membrane. The membrane was blocked in tris-buffered saline (TBS) buffer containing 5% skim milk and 0.1% Tween 20 at room temperature for 1 h and incubated withApo-A1 and Apo-A2 primary antibodies supplied by Novex overnight at pH 7.6 at 4 °C with gentle shaking. After washing, peroxidase-labeled secondary antibodies were added, and the membranes were incubated at 37 °C for 1 h. Band intensity was analyzed by ChemiDocTM imaging system with Image LabTM software version 5.1 (Bio-Rad Laboratories Inc., Hercules, CA, USA). Total proteins normalization was used to normalize each target protein levels. Apo-A1 monoclonal antibody was obtained from Novex, Catalogue number 701239. Apo- Apo-A2 monoclonal antibody was obtained from Novex Catalogue number 701236. Dilution of Apo-A1 antibodies used is 1: 3000, dilution ofApo-A2is 1: 3000, and final concentration is 2 µg/mL for all antibodies. Rat anti-mouse secondary antibody Horse Radish Peroxidase conjugate was obtained from ThermoFisher Scientific (USA, Rockford) Catalogue number 18-4015-82. Detection of proteins blots in PVDF membranes was conducted by Chemiluminescent Detection (Immun-Star™ WesternC™ Chemiluminescence Kit, Catalogue No. 1705061, BIO-RAD, USA). Protein standards for western Blot were obtained from Bio-Rad Precision plus western C protein standards Catalogue No. 161-0385. http://www.biorad.com/en-eg/applications-technologies/detection-methods#3Chemiluminescence detection was conducted using ChemiDocMP imaging system with Image Lab software version 5.1 (Bio-Rad, USA).

2.3. Statistical analysis

Data were analyzed by Sigma Plot version 12.5. Data was summarized as mean ± SD. Differences between groups were analyzed by (Kruskal-Wallis test) and (Shapiro-Wilktest) and *t*-test. Post-hoc testing was performed by the Tukey test to compare the difference among the groups. Simple linear correlation (Pearson correlation coefficient test) (r) was also done to test for linear relations between Apo-A1 and Apo-A2 and other variables. P-value is considered significant if < 0.05. Receiver operating characteristics curves (ROC curves) were utilized to assess diagnostic performance of all studied parameters.

3. Results

3.1. Biochemical characteristics of the studied subject

Demographic and clinico-pathological variables of all groups of the study are: Group-1 was composed of 12 females (24%) and 38 males (76%). The history of smoking variable was significantly higher in malignant patients group ($p = 0.002$). The frequencies of bilharzia in patients with malignant group were (36%). Histopathologic examination of bladder carcinoma tissues revealed: transitional cell carcinoma (TCC) in 36 cases (72%) and squamous cell carcinoma (SCC) in 14 cases (28%). Regarding the tumor stage, the frequencies of non-muscle (Ta-T1&T2) – and muscle-invasive tumors (T3-T4) were 58% and 42%, respectively. Regarding tumor grade, those frequencies of G1, G2 were 50%, also G3, were, 50%. Group-2 was composed of 10 females (20%) and 40 males (80%). The history of smoking variable was 60% in benign group patients. The frequencies of bilharzia in benign group patients were (20%). Group-3 was composed of 6 females (12%) and 44 males (88%). There is no history of smoking or bilharzia infection.

3.2. Blood and urine protein levels of Apo-A1 and Apo-A2

Blood and urine protein levels of Apo-A1 and Apo-A2 assessed by total protein normalization ratio in the all studied groups are shown in Table 1 and Figs. 1–4. Apo-A1 and Apo-A2 expression in urine of cancer patients (malignant group) showing high significant elevation in comparison to normal (control) and benign groups. Apo-A1 and Apo-A2 expression in blood of cancer patients (malignant group) showing no significant difference from normal (control).

3.3. Receiver operating characteristics (ROC) curves

Receiver operating characteristics curves were carried out to assess the diagnostic performance of Apo-A1 and Apo-A2 and their Sensitivity (true positive fraction) and Specificity (false positive fraction (Table 2) (Figs. 5 and 6)).

Table 3 showed correlation of urinary levels of Apo-A1 and Apo-A2 with their corresponding blood levels and also correlation of urinary levels of Apo-A1 and Apo-A2 with laboratory data of all malignant

Table 1
Blood and urine levels of Apo-A1 and Apo-A2 in all groups of the study assessed by western blot.

Parameter	Malignant group	Benign group	Normal group	p- value
Ratio of Apo-A1 in urine	464.8 ± 46.1[a,b]	59.1 ± 11.2[a]	0.0 ± 0.0	p < 0.001
Ratio of Apo-A1 in blood	1.0 ± 0.2	1.5 ± 0.2	0. 9 ± 0.1	p < 0.001
Ratio of Apo-A2in urine	93.6 ± 11.5[a,b]	39.9 ± 8.5[a]	0.0 ± 0.0	p < 0.001
Ratio of Apo-A2 in blood	1.0 ± 0.1	1.7 ± 0.1	0.9 ± 0.1	p < 0.001

[a] Significant from control.
[b] Significant from benign group.

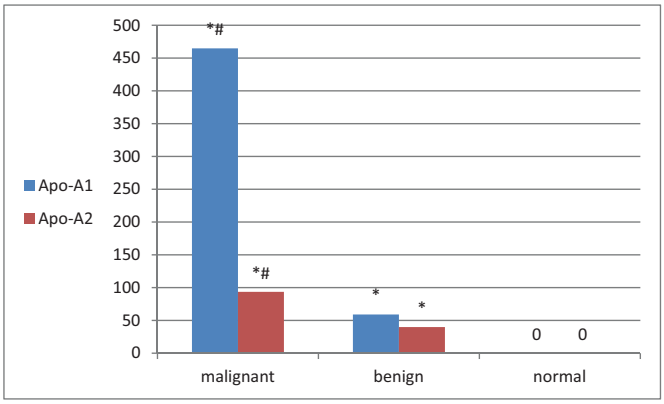

Fig. 1. Urinary protein levels of Apo-A1 and Apo-A2 in groups of the study by western blot. * denotes significant p versus control group, # denotes significant p versus benign bladder disorders group. Y axis represents a ratio between target protein levels and total protein level.

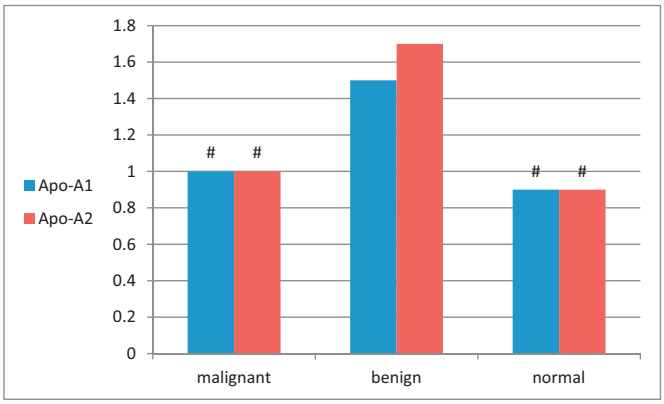

Fig. 2. Blood protein levels of Apo-A1 and Apo-A2 in groups of the study by western blot. * denotes significant p versus control group, # denotes significant p versus benign bladder disorders group. Y axis represents a ratio between target protein levels and total protein level.

group. There was no correlation between Apo-A1or Apo-A2 urine levels and their corresponding blood levels. Also there was no correlation between Apo-A1 and Apo-A2 urinary levels and other laboratory data using Pearson correlation.

Table 4 showed the correlation between urinary levels of Apo-A1 and Apo-A2 and different clinic-pathological parameters in bladder cancer (malignant) group.

4. Discussion

There is still a major need for reliable and specific biomarker for the early diagnosis of bladder cancer. Thus, noninvasive urine cytology may be of a good use in the clinic as a cystoscopy assistant; however, it's low sensitivity as a drawback (6). Here, a brand new noninvasive, label-free technique with higher sensitivity for use with urine is introduced (Yosef et al., 2017).

Proteomics has been adequately utilized for human-based investigations from claiming disease, where it has been a profitable approach for distinguishing diseases even more generating candidate biomarkers to identify pathological state (Sotillo et al., 2015).

Apo-A1, which mediates the reverse transport of cholesterol from peripheral cells to the liver for excretion, is a major high-density lipoprotein (HDL) component in plasma, constituting about 70% of the apolipoprotein (APO) content of HDL particles. In the lipid-bound state, Apo-A1 governs lipid transport, receptor recognition and other functions, including activation of lecithin-cholesterol acyltransferase, which converts cholesterol to cholesterol ester (Sengupta and Mukhopadhyay, 2016). Apo-A2 is the second-most abundant apolipoprotein of HDL 20% of HDL protein (Moradi et al., 2017).

The diagnostic value of Apo-A1 in early tumor detection was reported in many subsequent studies in which, increased levels of Apo-A1 were found in various malignant tumors. Apo-A1 precursor was significantly increased suggesting it could be an effective potential biomarker in the diagnosis of thyroid cancer (Li et al., 2014).

In cancer, lipid and cholesterol homeostasis is often dysregulated to facilitate the cancer cells' increased demand for these building blocks which are required for proliferation and evasion of apoptosis. To this end, tumor cells can manipulate their intracellular cholesterol level by reducing expression of ABCA1 which effluxes cholesterol and increasing the expression of SR-B1 which influxes cholesterol. This phenomenon has been reported in several prostate, colon and bladder cancers.

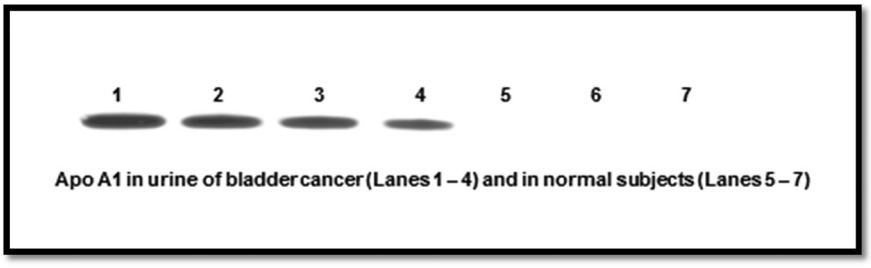

Fig. 3. Levels of Apo-A1 expression by protein normalization ratio in urine samples of the studied group.

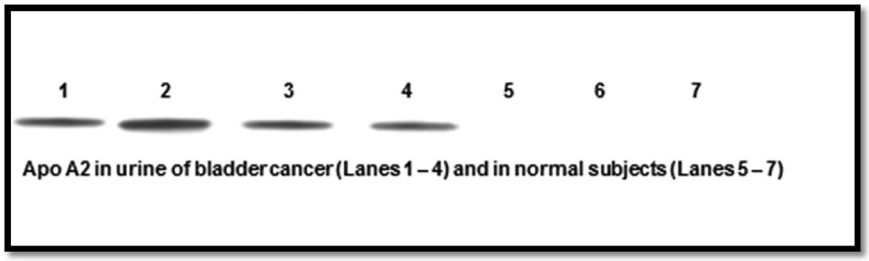

Fig. 4. Levels of Apo-A2 expression by protein normalization ratio in urine samples of the studied groups.

The present study showed that the level of Apo-A1 and Apo-A2 in voided urine was significantly higher in malignant group than cystitis (benign) group and normal healthy group with 100% sensitivity and 100% specificity for both markers and 100% PPV and 100% NPV and 100% AUC for two markers. This result was in agreement with many studies. Li et al., have reported that Apo-A1 was detected in all urine's samples (n = 40) of bladder cancers (Li et al., 2014). In another study they found that Apo-A1 have higher level in urine from bladder cancer patients (Hammam et al., 2015). Similarly, Chen et al., found that the average levels of Apo-A1, Apo-A2 were high in cancer group compared to controls (Chen et al., 2010). In another study they found that 12 proteins including Apo-A1 and Apo-A2 represent potential urinary biomarker candidates for detection of bladder cancer (Chen et al., 2012). In another study, apolipoproteins Apo-A1 and Apo-A2, were present at elevated levels in bladder cancer urine specimens (Chen et al., 2013). Results also showed that both Apo-A1 and Apo-A2 levels in blood of three groups were measured without any significant difference between normal and bladder cancer group. At the present time, we do not know the mechanism involved significantly increased of urinary ApoA1 and ApoA2 in bladder cancer, while not changed in the blood. Further studies of these markers on large number of patients along with follow-up of the patients for tumor recurrence are recommended.

5. Conclusion

This study revealed that Apo-A1 and Apo-A2 protein levels in urine could be used as a reliable diagnostic agent as well as screening biomarker which is characterized with being highly sensitive and non-invasive.

Informed consent

Each subject signed an informed consent before participating to the study.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

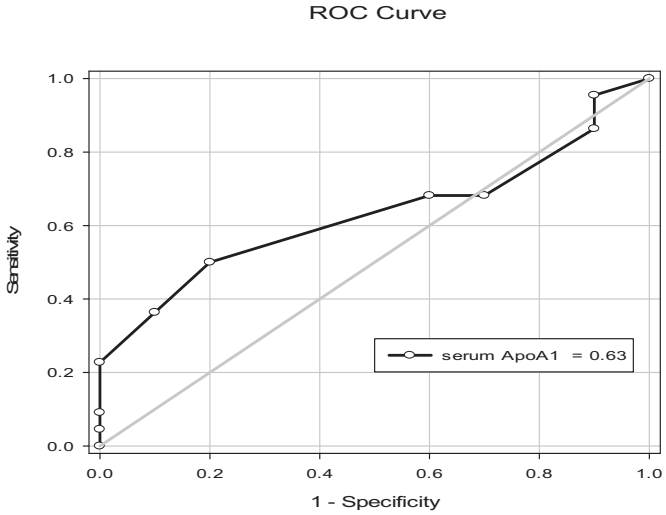

Fig. 5. Roc curve of ApoA1 in blood.

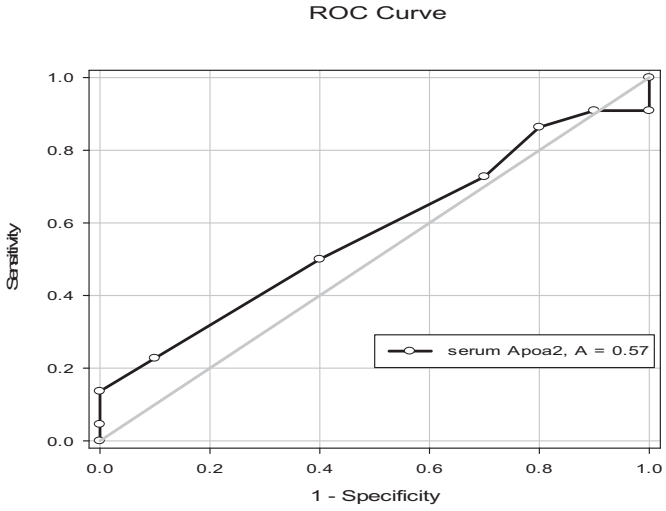

Fig. 6. Roc curve of ApoA2 in blood.

Table 2
Data of ROC curves of Apo-A1 and Apo-A2 in urine and blood.

ROC	Cut off value	Sensitivity	Specificity	Positive predictive value (PVP)	Negative predictive value (NPV)	AUC*
Apo-A1 in urine	195.6	100%	100%	100%	100%	100%
Apo-A1 in blood	1.2	22.7%	100%	100%	96%	62.9%
Apo-A2 in urine	40.0	100%	100%	100%	100%	100%
Apo-A2 in blood	1.2	13.6%	100%	100%	95.6%	57%
Combination (ApoA-1 + Apo-A2 in blood)	1.4	18.8%	100%	100%	95.8%	60.6%

AUC* represent accuracy.

Table 3
Correlations between urinary Apo-A1and Apo-A2 as well as other laboratory data of all malignant group.

Variables	Urinary Apo-A1		Urinary Apo-A2	
	R	p-value	R	p-value
Serum ratio of the marker	−0.18	p > 0.05	−0.23	p > 0.05
Serum Urea (mg/dl)	−0.15	p > 0.05	0.03	p > 0.05
Creatinine (mg/dl) Serum	0.10	p > 0.05	0.18	p > 0.05
Albumin (mg/dl) Serum	−0.07	p > 0.05	0.15	p > 0.05
Serum AST (IU/L)	−0.07	p > 0.05	−0.27	p > 0.05
Serum ALT (IU/L)	−0.11	p > 0.05	−0.07	p > 0.05
Serum ALP (IU/L)	0.06	p > 0.05	−0.24	p > 0.05
Serum Na (mEq/l)	−0.30	p > 0.05	0.12	p > 0.05
Serum K (mEq/l)	−0.009	p > 0.05	−0.02	p > 0.05

Table 4
Correlation of urinary levels of ApoA-1and Apo-A2 with clinic-pathological parameters in the malignant group (n = 50) using *t*-test:

Clinicopathological factor	Mean ± SD of urinary Apo-A1	P value of urinary Apo-A1	Mean ± SD of urinary Apo-A2	P value of urinary Apo-A2
Sex				p > 0.05
Male	463.2 ± 43.6	p > 0.05	93.2 ± 12.9	
Female	470.0 ± 61.3		95.0 ± 6.1	
Smoking				p > 0.05
Smoker	461.9 ± 44.7	p > 0.05	92.3 ± 11.8	
Non-Smoker	468.8 ± 51.6		95.5 ± 11.8	
Bilharziasis				p > 0.05
Bilharzial	465.0 ± 50.3	p > 0.05	90.6 ± 10.8	
Non bilharzial	464.6 ± 46.3		95.3 ± 12.1	
Type				p > 0.05
TCC	470.0 ± 45.5	p > 0.05	94.6 ± 12.5	
SCC	450.8 ± 50.8		90.8 ± 9.1	
Grade				p > 0.05
Low (1&2)	474.0 ± 31.1	p > 0.05	94.0 ± 12.4	
High (3)	455.4 ± 58.3		93.1 ± 11.4	
Stage				p > 0.05
Early (a, 1&2)	475.5 ± 44. 1	p > 0.05	93.3 ± 12.6	
Late (3&4)	457.3 ± 50.6		93.8 ± 10.8	

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Declaration of Competing Interest

The authors declare no conflict of interest.

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Availability of data and materials

The data that support the findings of this study are available from the corresponding author on reasonable request.

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