Heliyon 10 (2024) e24456

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Association between CT-based adipose variables, preoperative blood biochemical indicators and pathological T stage of clear cell renal cell carcinoma

Zehua Sun [a,1], Yumei Zhang [a,1], Yuanhao Xia [a,b,1], Xinru Ba [c,1], Qingyin Zheng [d], Jing Liu [e], Xiaojing Kuang [f], Haizhu Xie [a], Peiyou Gong [a], Yinghong Shi [a], Ning Mao [a], Yongtao Wang [a], Ming Liu [a], Chao Ran [a], Chenchen Wang [a], Xiaoni Wang [a], Min Li [g], Wei Zhang [h], Zishuo Fang [i], Wanchen Liu [a], Hao Guo [a,*], Heng Ma [a,**], Yang Song [j,***]

[a] Department of Radiology, Yantai Yuhuangding Hospital, Qingdao University School of Medicine, Yantai, 264000, Shandong, China
[b] Department of Radiology, Binzhou Medical University, Yantai, 264000, Shandong, China
[c] Department of Radiology, Yantaishan Hospital, Yantai, 264000, Shandong, China
[d] Department of Otolaryngology-Head & Neck Surgery, Case Western Reserve University, Cleveland, OH, 44106, United States
[e] Department of Pediatrics, Yantai Yuhuangding Hospital, Qingdao University School of Medicine, Yantai, 264000, Shandong, China
[f] School of Basic Medicine, Qingdao University, Qingdao, 266021, Shandong, China
[g] Department of Radiology, Yantai Traditional Chinese Medicine Hospital, Yantai, 264000, Shandong, China
[h] Department of Radiology, Yantai Penglai People's Hospital, Yantai, 265600, Shandong, China
[i] School of Electronic Science and Engineering, University of Electronic Science and Technology of China, Chengdu, 610000, China
[j] Department of Nutrition and Food Hygiene, School of Public Health, College of Medicine, Qingdao University, Qingdao, 266021, Shandong, China

ARTICLE INFO

Keywords:
Clear cell renal cell carcinoma (ccRCC)
Pathological T stage
Adipose tissue
Blood chemical indicator
Computed tomography (CT)

ABSTRACT

Background: Clear cell renal cell carcinoma (ccRCC) is corelated with tumor-associated material (TAM), coagulation system and adipocyte tissue, but the relationships between them have been inconsistent. Our study aimed to explore the cut-off intervals of variables that are non-linearly related to ccRCC pathological T stage for providing clues to understand these discrepancies, and to effectively preoperative risk stratification.

Methods: This retrospective analysis included 218 ccRCC patients with a clear pathological T stage between January 1st, 2014, and November 30th, 2021. The patients were categorized into two cohorts based on their pathological T stage: low T stage (T1 and T2) and high T stage (T3 and T4). Abdominal and perirenal fat variables were measured based on preoperative CT images. Blood biochemical indexes from the last time before surgery were also collected. The generalized sum model was used to identify cut-off intervals for nonlinear variables.

Results: In specific intervals, fibrinogen levels (FIB) (2.63–4.06 g/L) and platelet (PLT) counts ($>200.34 \times 10^9$/L) were significantly positively correlated with T stage, while PLT counts ($<200.34 \times 10^9$/L) were significantly negatively correlated with T stage. Additionally, tumor-associated material exhibited varying degrees of positive correlation with T stage at different cut-off intervals (cut-off value: 90.556 U/mL).

* Corresponding author.
** Corresponding author.
*** Corresponding author.
E-mail addresses: guohao112@163.com (H. Guo), mahengyhdyy@163.com (H. Ma), qdsongyang@126.com (Y. Song).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.heliyon.2024.e24456
Received 4 October 2023; Received in revised form 2 January 2024; Accepted 9 January 2024
Available online 13 January 2024
2405-8440/© 2024 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Conclusion: Preoperative PLT, FIB and TAM are nonlinearly related to pathological T stage. This study is the first to provide specific cut-off intervals for preoperative variables that are nonlinearly related to ccRCC T stage. These intervals can aid in the risk stratification of ccRCC patients before surgery, allowing for developing a more personalized treatment planning.

1. Introduction

Clear cell renal cell carcinoma (ccRCC) accounts for approximately 85 % of all renal cell carcinomas and its global incidence is on the rise [1]. The coagulation system has been implicated in cancer development, with elevated levels of fibrinogen (FIB) and platelet (PLT) counts observed in various cancers, including renal cell carcinoma (ccRCC) [2–6]. These elevated levels may contribute to tumor growth, angiogenesis, and metastasis [2–6]. Elevated pretreatment plasma FIB is significantly associated with decreased survival in patients with solid tumors, with the highest negative effect observed in RCC [4]. Additionally, certain genetic factors related to PLT or FIB receptors have been associated with an increased likelihood of metastasis in RCC [6]. Tumor-associated material (TAM) containing sialic acid (SA) and hydroxyproline (Hyp) also serve as important biomarkers in cancer development, as evidenced by previous reports [7–11].

Obesity has also been linked to the course and outcome of ccRCC, with abdominal fat influencing the occurrence and progression of the tumor [12]. Abdominal visceral fat has been identified as a reliable predictor of T stage in ccRCC [13,14]. Interaction between tumor cells and perirenal adipose tissue has been shown to facilitate ccRCC growth, invasion, and metastasis [15]. Therefore, accurate measurement of abdominal fat and perirenal fat levels is the premise for risk stratification regarding ccRCC pathological T stage. However, some studies have reported conflicting results regarding the association between fat-related parameters and T stage in different cancer types [16–19], highlighting the complex role of adipocyte tissue in cancer risk. For example, the increased retroperitoneal fat thickness did not appear to be associated with a higher T stage or N stage in 83 cases of non-metastatic colon cancer,

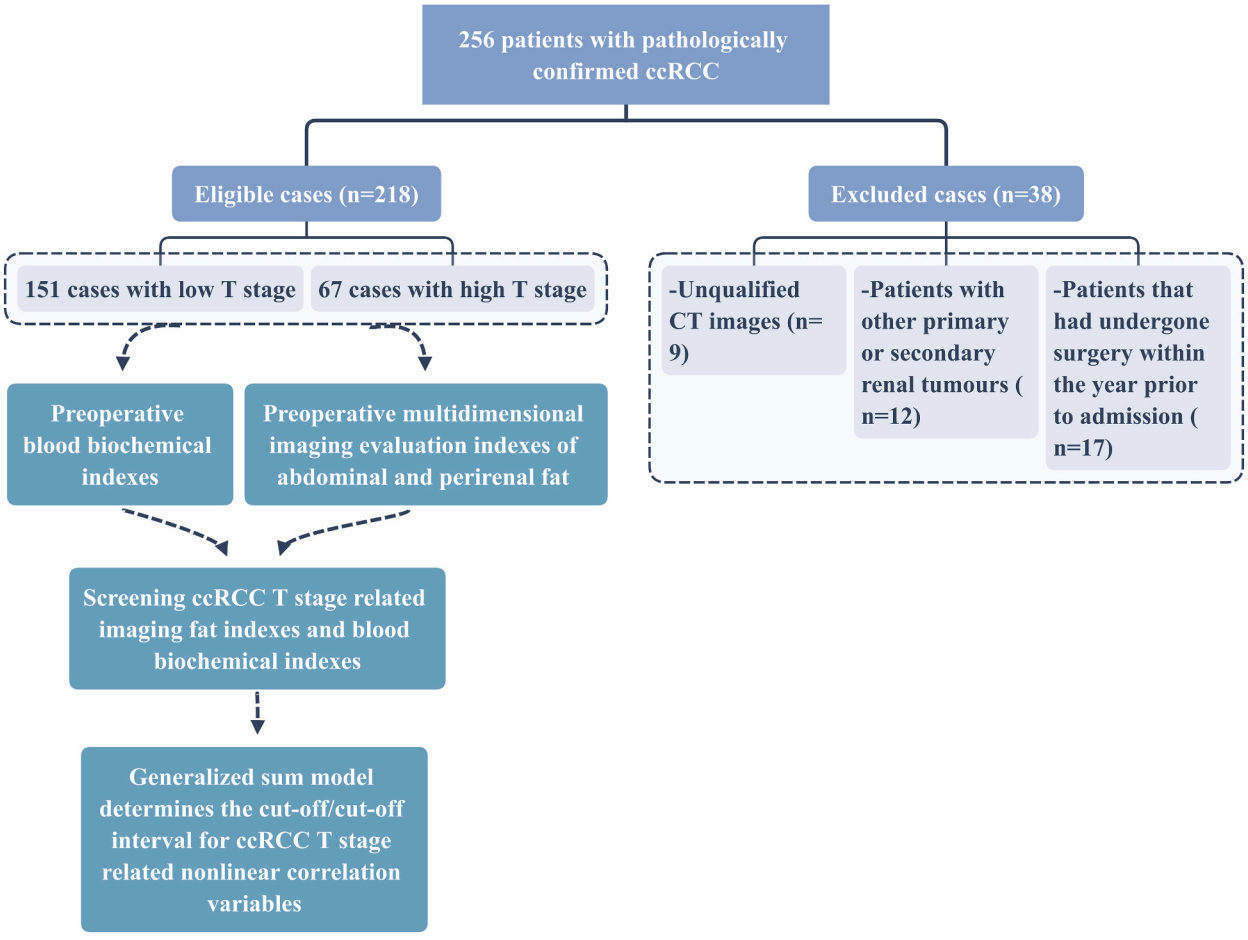

Fig. 1. Overview of the design and patients' enrollment. ccRCC = clear cell renal cell carcinoma.

based on observational studies of 83 cases [18]. Conversely, the proportion of fat around the tumor is positively associated with the axillary lymph node involvement demonstrated in patients with early-stage (T1 and T2) breast cancer [19]. Aside from methodological differences, the differences between studies may also reflect obesity's complex role in cancer risk. Anyhow, cancer initiation and progression are influenced more by the tumor microenvironment [15]. To date, there has been a lack of clinical studies to explore the cut-off intervals of fat-related parameters obtained via CT images that are non-linearly related to the T stage of ccRCC.

Although accurately determining the T stage of ccRCC before surgery is crucial for guiding treatment decisions and improving patient outcomes, the existing research results are inconsistent [16–19], possibly due to the non-linear relationship between preoperative predictive indicators and T stage. This study aims to identify and establish the specific correlated intervals of clinical and imaging indicators that exhibit a non-linear association with ccRCC pathological T stage. Through these findings, the study provides valuable insights for clinicians to accurately stratify preoperative risks and develop precise, individualized treatment plans for ccRCC patients.

2. Patients and methods

2.1. Patients and ethics

The overview and patients' enrollment of this study are shown in Fig. 1. A total of 218 patients who were pathologically diagnosed with ccRCC between January 2014 and November 2021 at Yantai Yuhuangding Hospital were included in this retrospective study. Patients with other tumors, preoperative distress (such as type 1 and type 2 diabetes, metabolic disorders, chronic medication use), those who underwent surgery within one year prior to admission, and those with no available preoperative CT data were excluded. The study protocol was approved by the Ethics Committee of Yantai Yuhuangding Hospital (ID: 2021-323), and informed consent was waived.

2.2. Clinical data collection

Information including site, sex, age, body mass index (BMI), and preoperative blood biochemical indicators (using data from the last examination before surgery if multiple tests were performed) were collected. The patients were divided into two groups based on their ccRCC pathological T stage: low T stage (T1 and T2) and high T stage (T3 and T4) [20].

Abdominal and Perirenal Fat Measurement and Evaluation.

ImageJ 1.51 software was used to outline the area of interest along the abdominal wall muscle group at the umbilical level (yellow line), and the range of Hounsfield unit threshold was set from −150Hu to −50Hu [21]. Visceral fat area (VFA) and subcutaneous fat area (SFA) were measured separately (see Fig. 2A), and the total fat area (TFA) encompasses the sum of both visceral and subcutaneous

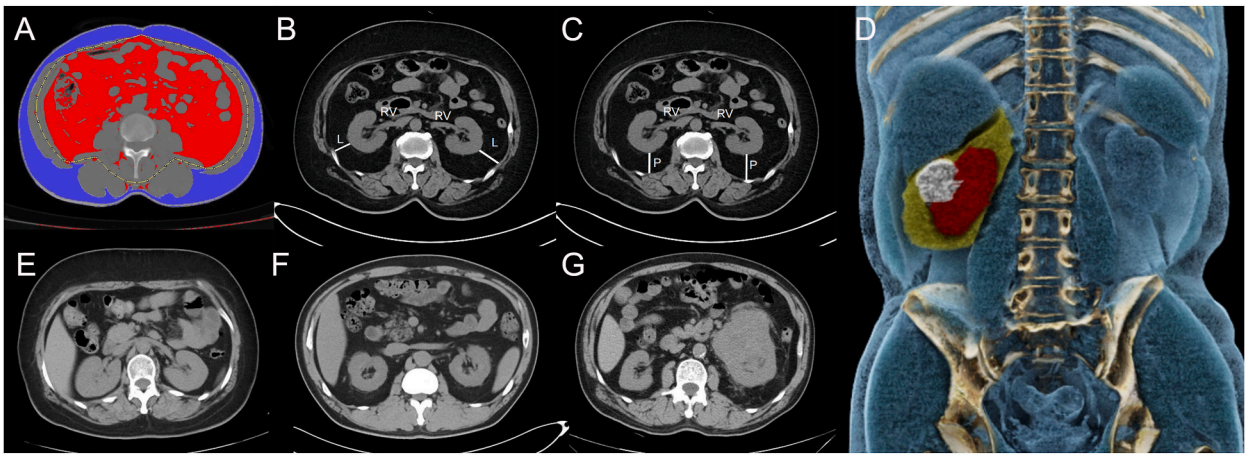

Fig. 2. The schematic representation of multidimensional imaging parameters. (**A**). Quantitative measurements of abdominal fat. A yellow line outlined the region of interest along the abdominal wall muscle group at the level of the umbilicus. The CT value range was set from −150 Hounsfield units (Hu) to −50 Hu. The red area represents the VFA, and the blue area represents the SFA. (**B**, **C**). The methods for measuring perinephric fat at the level of the renal vein. The abbreviation "L" stands for LPFT; "P" stands for PPFT, and "RV" represents the renal vein. d: Measurement of PFV. (**D**) Perirenal fat (yellow), normal renal tissue (red), and tumor (white) based on segmentation using the syngo via workstation. (**E-G**). Grading of PFS. (**E**). Type 0 (none) - 0 points. The fat surrounding the kidney shows no stranding, and the tissue appears completely black on the CT image. (**F**). Type 1 (mild/moderate) - 2 points. Some image-dense stranding is present in the fat around the kidney, but there are no thick bars of inflammation. (**G**). Type 2 (severe stranding) - 3 points. The CT image shows severe stranding around the kidney with thick, image-dense bars of inflammation. VFA = visceral fat area; SFA = subcutaneous fat area; LPFT = Lateral perinephric fat thickness; PPFT = Posterior perinephric fat thickness; PFS = Perinephric fat stranding; PFV = Perirenal fat volume; PFS = perinephric fat stranding; CT = Computed tomography.

fat measurements.

Lateral perinephric fat thickness (LPFT) and posterior perinephric fat thickness (PPFT) were measured at the level of the renal vein from the preoperative CT images [22]. LPFT is defined as the measurement extending from the renal capsule to the sidewall in a parallel manner to the renal vein (see Fig. 2B). PPFT is defined as the measurement represented by a direct line drawn from the renal capsule to the posterior abdominal wall (see Fig. 2C). The presence of perinephric fat stranding (PFS) was observed and graded for each affected kidney based on CT images, characterized as a linear region of soft tissue density within the perinephric space as shown in Fig. 2E–F [23].

The perirenal fat volume (PFV) was automatically measured using regional growth module of the workstation (Syngo workstation, VB 30; Siemens Healthcare Solutions, Erlangen, Germany) as shown in Fig. 2D. The perirenal fascia contours were manually plotted on each layer's image from the cranial to caudal boundaries. The cranial and caudal boundaries of PFV were determined based on the visible Gerota fascia in the respective CT images. An automated calculation analysis then obtained the volume of interest - PFV within the Hounsfield unit threshold range of −150Hu to −50Hu [21].

Two experienced senior radiologists with over ten years of experience ensured the reliability of measurements, resolving uncertainties through consensus and consultation another senior radiologist. The schematic representation of multidimensional imaging

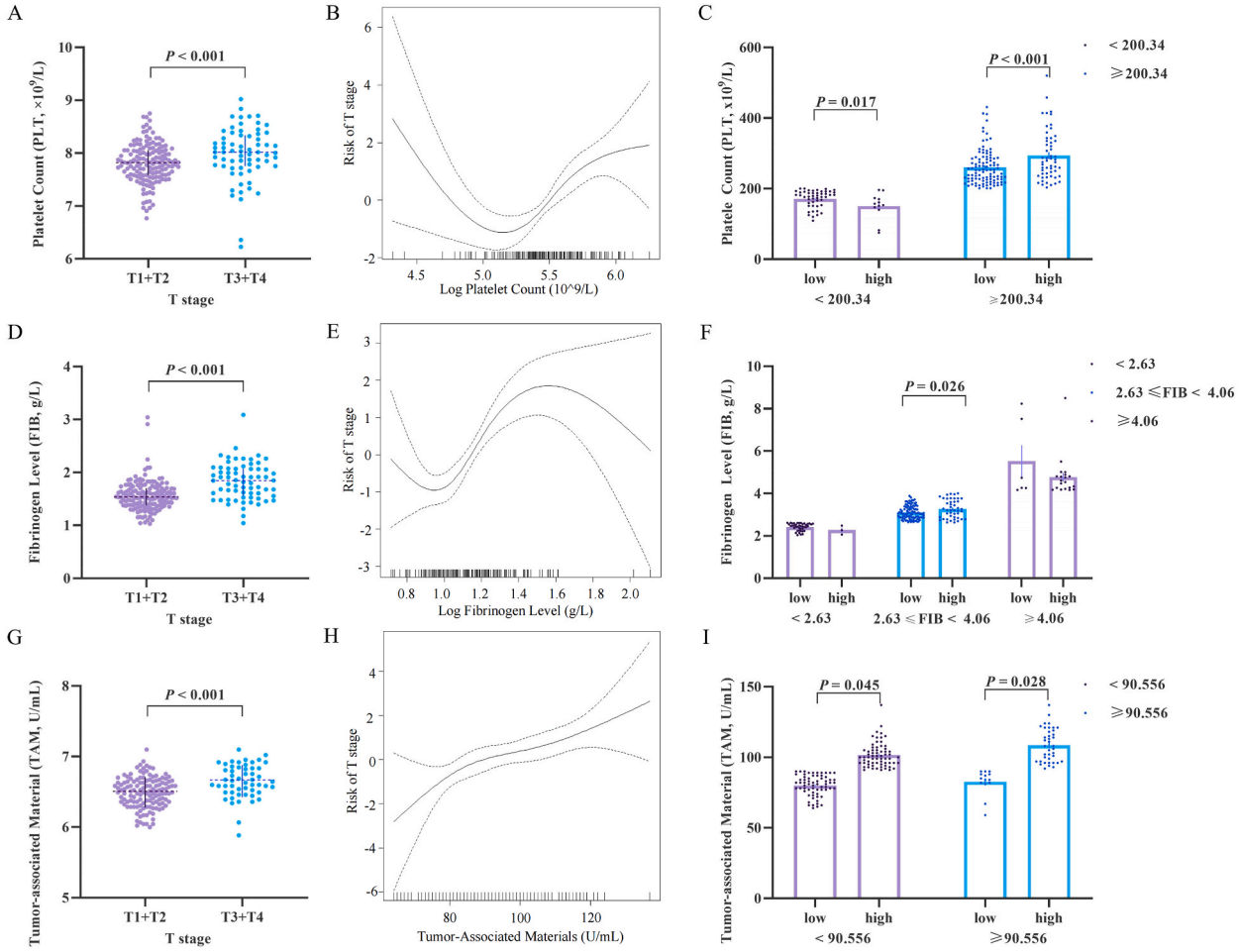

Fig. 3. Nonlinearly correlated variables and their cut-off values/intervals with ccRCC T stage after adjusting for site, gender, age, BMI, and preoperative comorbidities. Preoperative biochemical parameters showing a significant positive correlation with ccRCC pathological T stage in the panel (**A**) PLT, (**D**) FIB, and (**G**) TAM. (**B, C**). Preoperative PLT counts. The plots illustrated the prevalence of T stage before and after the turning point ($Log_e^{PLT} = 5.3$, i.e., PLT = 200.34×10^9/L). Before the turning point, the prevalence of high T stage (T3 and T4) was lower, but after the turning point, the prevalence of high T stage increased significantly. (**E, F**). Preoperative FIB levels. The plots shown indicated a positive correlation between elevated FIB levels and T stage, when the preoperative FIB level fell within the specified cut-off interval ($0.967 < Log_e^{FIB} < 1.400$, i.e., 2.63 g/L ≤ FIB <4.06 g/L). (**H, I**). Preoperative TAM level. The plots demonstrated that the increase in preoperative TAM level showed a positive correlation with T stage. This correlation holds true for TAM level both above the cut-off value (TAM >90.556 U/mL) and below the cut-off value (TAM <90.556 U/mL). Data in 3A and 3D are presented as median ± IQR, while data in 3G are presented as mean ± SD. Data for the remaining panels are presented as mean with SEM. ccRCC = clear cell renal cell carcinoma; PLT = platelet; TAM = tumor-associated material; FIB = fibrinogen; IQR = interquartile range; SD = standard deviation; SEM = standard error of the mean.

parameters is shown in Fig. 2.

2.3. Statistical analysis

Categorical data were described using percentages and analyzed using the chi-square test. Continuous data were tested for normal distribution and logarithmic transformation was applied if they did not conform to normal distribution. Student's *t*-tests (with normal distributions) and the Mann-Whitney *U* test (with non-normal distributions) were used to test for differences in continuous variables between the low and high T stage groups. A nonlinear test was conducted on relevant variables, and a generalized linear analysis was performed to determine the cut-off values or intervals of variables that had nonlinear correlations with the ccRCC T stage.

All statistical analyses, including two-tailed t-tests, were conducted using R 4.03 software, and a *P*-value less than 0.05 was considered statistically significant.

Table 1
General characteristics of ccRCC patients in the study cohort (n = 218).

Variable	Overall (n = 218)	T1-2 (n = 151)	T3-4 (n = 67)	Adjusted *P*-value
T stage, n (%)				
T1-2	151 (69.3)	151 (100.0)	0 (0.0)	**<0.001**[a]
T3-4	67 (30.7)	0 (0.0)	67 (100.0)	
Site, n (%)				
Left	112 (51.4)	69 (45.7)	43 (64.2)	**0.018**[a]
Right	106 (48.6)	82 (54.3)	24 (35.8)	
Gender, n (%)				
Female	66 (30.3)	51 (33.8)	15 (22.4)	0.126[a]
Male	152 (69.7)	100 (66.2)	52 (77.6)	
Preoperative comorbidities, n (%)				
Without	123 (56.4)	85 (56.3)	38 (56.7)	1.000[a]
With	95 (43.6)	66 (43.7)	29 (43.3)	
Age at operation, year				
	58.88 ± 10.07	57.51 ± 10.32	61.97 ± 8.79	**0.002**[b]
BMI, kg/m^2				
	24.84 ± 4.04	25.16 ± 4.16	23.99 ± 3.59	0.063[b]
Fibrinogen (FIB) levels, g/L				
	3.04 (2.69, 3.52)	2.90 (2.60, 3.24)	3.59 (2.99, 4.19)	**<0.001**[c]
Platelet (PLT) count, $\times 10^9/L$				
	233.00 (196.00, 281.25)	226.00 (192.00, 266.00)	259.00 (216.00, 322.00)	**0.001**[c]
Tumor-associated material (TAM), u/mL				
	94.06 ± 15.00	90.95 ± 13.45	101.75 ± 15.96	**<0.001**[b]
Perirenal fat volume (PFV), cm^3				
	230.56 (146.36, 353.28)	215.49 (139.03, 325.92)	248.31 (183.48, 415.94)	0.063[c]
Posterior perinephric fat thickness (PPFT), cm				
	1.00 (0.52, 1.58)	1.00 (0.60, 1.50)	1.00 (0.40, 1.60)	0.780[c]
Lateral perinephric fat thickness (LPFT), cm				
	1.35 (0.90, 2.10)	1.30 (0.85, 2.10)	1.50 (0.95, 2.15)	0.403[c]
Perinephric fat stranding (PFS), n (%)				
0	77(35.3)	70(46.4)	7(10.4)	**<0.001**[a]
2	129(59.2)	80(53.0)	49(73.1)	
3	12(5.5)	1(0.7)	11(16.4)	
Total fat area (TFA), cm^2				
	324.06 ± 122.23	334.94 ± 123.53	299.54 ± 116.44	**0.048**[b]
Visceral fat area (VFA), cm^2				
	130.65 (98.27, 171.86)	130.53 (95.27, 171.65)	130.68 (104.67, 177.93)	0.982[c]
Subcutaneous fat area (SFA), cm^2				
	184.84 (84.93)	194.67 (88.02)	162.70 (73.41)	**0.010**[c]
Total cholesterol (TC), mmol/L				
	4.77 ± 1.08	4.86 ± 1.05	4.57 ± 1.14	0.069[b]
Triglycerides (TG), mmol/L				
	1.21 (0.81, 1.70)	1.27 (0.84, 1.81)	1.08 (0.80, 1.54)	0.065[c]
HDL cholesterol (HDL-C), mmol/L				
	1.21 (1.04, 1.43)	1.26 (1.07, 1.48)	1.15 (1.00, 1.30)	**0.001**[c]
LDL cholesterol (LDL-C), mmol/L				
	2.98 ± 0.86	2.99 ± 0.85	2.95 ± 0.90	0.783[b]
Lipoproteins, mg/L				
	171.50 (85.25, 334.75)	140.00 (73.50, 280.00)	232.00 (121.00, 424.50)	**0.001**[c]

$P < 0.05$ is indicated by boldface.
[a] Chi-squared test.
[b] Student's t-test.
[c] Mann–Whitney *U* test. BMI = Body mass index.

3. Results

3.1. General characteristics

A total of 218 patients with pathologically diagnosed ccRCC (152 males and 66 females) were enrolled in the study, of which 151 had low T stage (T1 and T2) and 67 had high T stage (T3 and T4) ccRCC.

After adjusting for site, gender, preoperative comorbidities, age, and BMI, patients with low T stage ccRCC had greater preoperative TFA (334.94 vs. 299.54, $P = 0.048$), SFA (194.67 vs. 162.70, $P = 0.01$), and HDL-C (1.26 vs. 1.15, $P = 0.001$) compared to those with high T stage ccRCC.

Conversely, patients with high T stage ccRCC showed significant increases in preoperative PLT counts (259.00 vs. 226.00, $P = 0.001$, see Fig. 3A), FIB levels (3.59 vs. 2.90, $P < 0.001$, see Fig. 3D), TAM (90.95 vs. 101.75, $P < 0.001$, see Fig. 3G), and lipoprotein levels (232.00 vs. 140.00, $P = 0.001$) (Table 1 and Fig. 3).

3.2. Non-linear variables and the corresponding cut-off values

Nonlinear tests showed that PLT, FIB, and TAM were non-linearly correlated with ccRCC T stage (Table 2).

The generalized sum model was used to determine the cut-off intervals for these variables (Table 3 and Fig. 3):

Preoperative PLT (Fig. 3B): The turning point was Log_e PLT = 5.3 (PLT = 200.34 × 10^9/L). Before this point (PLT <200.34 × 10^9/L), the prevalence of high T stage significantly decreased with increasing PLT count ($\beta = -4.989$, $P = 0.017$; OR 0.007; 95 % CI: 0.000–0.412), but after this point (PLT >200.34 × 10^9/L), it increased significantly with increasing PLT levels ($\beta = 3.284$, $P = 0.001$; OR 26.675; 95 % CI: 3.934–180.868) as shown in Fig. 3C.

Preoperative FIB (Fig. 3D): Increased FIB level was positively correlated with high T stage when the FIB level was in the cut-off interval ($0.967 < Log_e^{FIB} < 1.400$, i.e., 2.63 g/L ≤ FIB< 4.06 g/L; $\beta = 4.308$, $P = 0.026$; OR 74.302; 95 % CI: 1.671–3303.505) as shown in Fig. 3F.

Preoperative TAM (Fig. 3H): The increase in preoperative TAM level showed a positive correlation with T stage both above (TAM >90.556 U/mL; $\beta = 0.051$, $P = 0.028$; OR 1.052; 95 % CI: 1.005–1.102) and below (TAM <90.556 U/mL; $\beta = 0.127$, $P = 0.045$; OR 1.135; 95 % CI: 1.003–1.285) the cut-off value as shown in Fig. 3I.

Other variables, such as PFV, VFA, SFA, and lipoprotein levels, did not show significant nonlinear correlations with ccRCC T stage.

4. Discussion

This study identified several indexes that were significantly higher in clear cell renal cell carcinoma (ccRCC) patients with high T stage. These included coagulation system-related indexes (fibrinogen and platelet counts), tumor-related indicators (tumor-associated material - TAM), and adipose-related parameters (perirenal fat stranding - PFS, and lipoproteins). However, it's worth noting that PFS showed a positive correlation with high T-stage, while other adipose-related parameters (total fat area - TFA, subcutaneous fat area - SFA, and high-density lipoprotein cholesterol - HDL-C) showed an inverse correlation with high T stage.

The present study used nonlinear tests to identify the relationships between certain indexes and ccRCC T stage. Specifically, fibrinogen (FIB), platelet (PLT), and TAM were found to be non-linearly correlated with T stage. This study further determined specific cut-off intervals for these variables, indicating the points at which their correlation with T stage changed significantly. For instance,

Table 2
Nonlinear correlation test of indexes on pathological T stage of ccRCC.

Variables	*x*2	Adjusted *P*-value
PFV*	0.899	0.826
TFA	2.734	0.434
VFA*	2.615	0.455
SFA*	2.371	0.499
VFA/TFA	2.836	0.418
FIB*	24.477	<0.001
PLT*	23.363	<0.001
TAM	13.682	0.003
TC	2.552	0.466
TG	4.135	0.247
HDL-C	7.765	0.051
LDL-C	2.291	0.514
Lipoproteins*	7.789	0.051

$P < 0.05$ is indicated by boldface.
*: log transformation. ccRCC = Clear cell renal cell carcinoma; PFV = Perirenal fat volume; TFA = Total fat area; VFA = Visceral fat area; SFA = Subcutaneous fat area; FIB = Fibrinogen; PLT = Platelet; TAM = Tumor-associated material; LPFT = Lateral perinephric fat thickness; PPFT = Posterior perinephric fat thickness; PFS = Perinephric fat stranding; HDL-C = High-density lipoprotein cholesterol; LDL-C = Low-density lipoprotein cholesterol.

Table 3
Threshold effect of nonlinear correlation variables on ccRCC pathological T stage.

	Crude			*Adjusted		
	ß	OR (95 % CI)	*P*	ß	OR (95 % CI)	*P*
FIB*, g/L						
FIB <0.967	−0.589	0.555(0.000,126119.642)	0.925	−1.377	0.252(0.000,181688.579)	0.841
0.967 ≤ FIB <1.4	4.886	132.419(4.564,3842.263)	**0.004**	4.308	74.302(1.671,3303.505)	**0.026**
FIB ≥1.4	−2.554	0.078(0.001,4.830)	0.225	−6.254	0.002(0.000,3.179)	0.098
PLT*, × 10^9/L						
PLT <5.3	−3.431	0.032(0.001,0.710)	**0.029**	−4.989	0.007(0.000,0.412)	**0.017**
PLT ≥5.3	2.771	15.968(2.874,88.727)	**0.002**	3.284	26.675(3.934,180.868)	**0.001**
TAM, U/mL						
TAM <90.556	1.053	(0.965,1.150)	0.247	1.135	(1.003,1.285)	**0.045**
TAM >90.556	1.070	(1.025,1.116)	**0.002**	1.052	(1.005,1.102)	**0.028**

$P < 0.05$ is indicated by boldface.
a: log transformation. ccRCC = clear cell renal cell carcinoma; FIB = fibrinogen; PLT = platelet; TAM = tumor-associated material.

PLT showed a dual role in ccRCC progression, being positively correlated with T stage when PLT was above a cut-off value and negatively correlated with T stage when PLT was below the cut-off value.

This study highlighted the complex relationship between obesity, adipose-related parameters, and ccRCC progression [16,17,24–28]. While some adipose-related indexes like PFS and lipoproteins were positively correlated with high T stage, other indexes like TFA, SFA, and HDL-C were higher in low T stage ccRCC patients. The findings are in line with previous studies indicating a potential protective role of obesity in early-stage kidney cancer but a more detrimental role in advanced-stage cancer [17,24–28]. Obesity promotes tumor progression at the local level by altering the microenvironment processes in the adipose tissue [15]. Previous study has shown that renal cell carcinoma (RCC) patients with high PFS have a poor prognosis [27]. In addition to verifying the interactive communication between ccRCC tumor cells and adjacent perirenal adipose tissue, Wei et al. also demonstrated that parathyroid hormone-associated protein secreted by ccRCC tumor cells could promote browning of perirenal adipose tissue, and that adipose cells that had turned brown could promote or inhibit tumorigenesis or progression through feedback communication [15]. This may explain the positively relationship of higher PFS in the high T stage cohort in this study. Some scholar believes that lipoprotein is significantly expressed in the high T-stage in order to synthesize more cell membrane lipids to meet the rapid growth of cancer cells and their soaring energy requirements [28].

In contrast, previous reports have indicated that obesity and certain lipid metabolism-related indexes (TFA, SFA, and HDL-C) play a protective role in tumor progression [17,24–26], corroborating our findings where these three indexes were significantly higher in the low T stage cohort. Studies involving RCC patients with obesity have demonstrated significantly improved overall survival, cancer-specific survival, and recurrence-free survival [24,25]. Additionally, a large clinical study of US ccRCC patients treated with surgery revealed that obese and overweight individuals had a lower incidence of advanced-stage and advanced-grade cancers compared to normal-weight patients [17]. Moreover, Posch et al. unveiled a positive correlation between subcutaneous adipose tissue index and survival in 1473 patients with gastrointestinal cancer and 273 patients with metastatic RCC, as assessed through CT imaging [26]. Notably, decreased serum HDL-C levels (<30 mg/dL) in women were also linked to increased cancer-related mortality [25]. These valuable insights collectively suggest a potential interplay between obesity and specific lipid metabolism-related indexes that may contribute to the protective effect against tumor progression, supporting the notion put forth in earlier research [17,24–26]. These findings underscore the potential significance of these indexes as prognostic factors in ccRCC.

This study reinforced the importance of the coagulation system and TAM in ccRCC progression. Elevated FIB and PLT levels were positively correlated with high T stage, and the interplay between these factors and TAM may promote tumor growth, invasion, and metastasis [2,29,30]. First, tumor cells produce various pro-inflammatory cytokines and chemokines, such as interleukin-6, tumor necrosis factor-alpha, and vascular endothelial growth factor (VEGF) [29]. Then these factors and various glycan proteins highly expressed on the surface of tumor cells, such as sialic acid (SA), stimulate the production of coagulation factors such as FIB and PLT [7,9]. Prior studies have shown that FIB, PLT, and inflammatory factors, along with VEGF, are closely related to vascular production, supporting tumor growth by supplying nutrients and oxygen to tumor cells [29]. Besides, FIB and PLT also interact with each other to enhance the migration, invasion, and metastasis of RCC cells by activating the epithelial-to-mesenchymal transition [30]. Several studies have shown that elevated FIB and PLT before surgery are associated with significantly increased distant metastasis and reduced survival in patients with solid tumors [2]. Hydroxyproline (Hyp) is an amino acid in TAM that is also an essential amino acid for extracellular matrix of tissues [8]. Elevated Hyp is observed in various cancers, such as epiterchiasis-associated cholangiocarcinoma [8]. By clumping together with tumor cells, FIB, PLT, and lymphocyte protect tumor cells of ccRCC from the immune system, and promote their retention in the capillaries [30]. In short, the interaction between the coagulation system and TAM in the proliferation, invasion, and spread of renal cancer cells has played a role in promoting the progression of RCC [8]. What was observed in our study is consistent with the findings mentioned above: patients with high T stage ccRCC tend to have higher coagulation factors (FIB, PLT), and TAM.

This study highlighted the clinical relevance of the identified cut-off intervals for FIB, PLT, and TAM, which can help in accurately stratifying ccRCC patients before surgery. These routine blood tests are convenient, reproducible, cost-effective, and clinically practical [31]. Accurate risk stratification can aid clinicians in developing personalized treatment plans for patients.

However, a notable limitation is the study's single-center design, which may have selection bias. Additionally, only patients with preoperative CT images were included, potentially limiting the generalizability of the findings. These issues require further multicenter prospective studies to validate the results.

5. Conclusion

In this retrospective study, we investigated the nonlinear relationship between preoperative clinically available indicators and pathological T stage in patients with ccRCC. Within specific intervals, we found significant positive correlations of FIB levels (2.63–4.06 g/L) and PLT counts ($>200.34 \times 10^9$/L) with pathological T stage, while PLT counts ($<200.34 \times 10^9$/L) showed a significant negative correlation with pathological T stage. Moreover, TAM exhibited varying degrees of positive correlation with pathological T stage at different cut-off intervals (cut-off value: 90.556 U/mL). Notably, to the best of our knowledge, this is the first study to confirm these specific intervals. These findings are valuable for risk stratification of ccRCC patients prior to surgery, enabling more personalized treatment plan making.

Funding

This study was supported by the Taishan Scholar Project (No. tsqn202103197), the Natural Science Foundation of Shandong Province (No. ZR2022MH274), the Yantai Science and Technology Innovation Development Project (No. 2023YD002), the Shandong Postdoctoral Science Foundation (SDCX-ZG-202303059), and the Beijing Science and Technology Innovation Medical Development Foundation (KC2023-JX-0186-BM084).

Data availability

Data are available for researchers who request it from the corresponding author (guohao112@163.com).

Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of Yantai Yuhuangding Hospital (ID: 2022-323), and informed consent was waived.

CRediT authorship contribution statement

Zehua Sun: Writing - review & editing, Writing - original draft, Visualization, Validation, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Yumei Zhang:** Writing - review & editing, Visualization, Validation, Data curation. **Yuanhao Xia:** Writing - original draft, Validation, Formal analysis, Data curation. **Xinru Ba:** Validation, Methodology, Investigation, Formal analysis, Data curation. **Qingyin Zheng:** Writing - review & editing, Supervision, Resources, Formal analysis. **Jing Liu:** Validation, Resources, Data curation. **Xiaojing Kuang:** Visualization, Validation, Resources. **Haizhu Xie:** Resources, Methodology, Investigation. **Peiyou Gong:** Validation, Resources. **Yinghong Shi:** Validation, Supervision, Resources. **Ning Mao:** Software, Resources, Methodology. **Yongtao Wang:** Visualization, Resources. **Ming Liu:** Visualization, Data curation. **Chao Ran:** Visualization, Data curation. **Chenchen Wang:** Software, Data curation. **Xiaoni Wang:** Software, Data curation. **Min Li:** Methodology, Data curation. **Wei Zhang:** Conceptualization. **Zishuo Fang:** Software, Methodology, Investigation, Data curation. **Wanchen Liu:** Formal analysis, Data curation. **Hao Guo:** Writing - review & editing, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Heng Ma:** Writing - review & editing, Validation, Supervision, Project administration, Conceptualization. **Yang Song:** Visualization, Supervision, Resources, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

Our thanks go to Wei Yue at Siemens (Jinan, 250000, China) for his assistance with image reconstruction.

List of abbreviations

ccRCC	Clear cell renal cell carcinoma
RCC	Renal cell carcinoma
PLT	Platelet
TAM	Tumor-associated material
FIB	Fibrinogen

BMI	Body mass index
CT	Computed tomography
VFA	Visceral fat area
SFA	Subcutaneous fat area
TFA	Total fat area
LPFT	Lateral perinephric fat thickness
PPFT	Posterior perinephric fat thickness
PFS	Perinephric fat stranding
PFV	Perirenal fat volume
PACS	Picture Archiving and Communication System
HDL-C	High-density lipoprotein cholesterol
LDL-C	Low-density lipoprotein cholesterol
SA	Sialic acid
Hyp	Hydroxyproline
VEGF	Vascular endothelial growth factor
IQR	Interquartile range
SD	Standard deviation
SEM	Standard error of the mean

References

[1] R.L. Siegel, K.D. Miller, H.E. Fuchs, A. Jemal, Cancer Statistics, CA Cancer J Clin 2021 71 (1) (2021) 7–33.
[2] M. Haemmerle, R.L. Stone, D.G. Menter, V. Afshar-Kharghan, A.K. Sood, The platelet lifeline to cancer: challenges and opportunities, Cancer Cell 33 (6) (2018) 965–983.
[3] M. Schlesinger, Role of platelets and platelet receptors in cancer metastasis, J. Hematol. Oncol. 11 (1) (2018) 125.
[4] C. Perisanidis, A. Psyrri, E.E. Cohen, J. Engelmann, G. Heinze, B. Perisanidis, et al., Prognostic role of pretreatment plasma fibrinogen in patients with solid tumors: a systematic review and meta-analysis, Cancer Treat Rev. 41 (10) (2015) 960–970.
[5] S. Erdem, A.S. Amasyali, O. Aytac, K. Onem, H. Issever, O. Sanli, Increased preoperative levels of plasma fibrinogen and D dimer in patients with renal cell carcinoma is associated with poor survival and adverse tumor characteristics, Urol. Oncol. 32 (7) (2014) 1031–1040.
[6] J.P. Kallio, J. Mikkelsson, T.L. Tammela, P.J. Karhunen, P. Kellokumpu-Lehtinen, Genetic variation in platelet integrin alphabeta (GPIIb/IIIa) and the metastatic potential of renal cell carcinoma, BJU Int. 98 (1) (2006) 201–204.
[7] F. Li, J. Ding, Sialylation is involved in cell fate decision during development, reprogramming and cancer progression, Protein Cell 10 (8) (2019) 550–565.
[8] S. Prakobwong, L. Charoensuk, Y. Hiraku, P. Pinlaor, C. Pairojkul, E. Mairiang, et al., Plasma hydroxyproline, MMP-7 and collagen I as novel predictive risk markers of hepatobiliary disease-associated cholangiocarcinoma, Int. J. Cancer 131 (4) (2012) E416–E424.
[9] A.C. Hernandez-Arteaga, J. de Jesus Zermeno-Nava, M.U. Martinez-Martinez, A. Hernandez-Cedillo, H.J. Ojeda-Galvan, M. Jose-Yacaman, et al., Determination of salivary sialic acid through nanotechnology: a useful biomarker for the screening of breast cancer, Arch. Med. Res. 50 (3) (2019) 105–110.
[10] N. Chiba, M. Sunamura, M. Nakagawa, I. Koganezawa, K. Yokozuka, T. Kobayashi, et al., Overexpression of hydroxyproline via EGLN/HIF1A is associated with distant metastasis in pancreatic cancer, Am. J. Cancer Res. 10 (8) (2020) 2570–2581.
[11] Y. Zhang, Z. Sun, H. Ma, C. Wang, W. Zhang, J. Liu, et al., Prediction of Fuhrman nuclear grade for clear cell renal carcinoma by a multi-information fusion model that incorporates CT-based features of tumor and serum tumor associated material, J. Cancer Res. Clin. Oncol. 149 (17) (2023) 15855–15865.
[12] B. Lauby-Secretan, C. Scoccianti, D. Loomis, Y. Grosse, F. Bianchini, K. Straif, et al., Body fatness and cancer–viewpoint of the IARC working group, N. Engl. J. Med. 375 (8) (2016) 794–798.
[13] H. Guo, Y. Zhang, H. Ma, P. Gong, Y. Shi, W. Zhao, et al., T-stage-specific abdominal visceral fat, haematological nutrition indicators and inflammation as prognostic factors in patients with clear renal cell carcinoma, Adipocyte 11 (1) (2022) 133–142.
[14] H. Guo, W. Zhao, A. Wang, M. Li, H. Ma, F. Wang, et al., The value of sex-specific abdominal visceral fat as measured via CT as a predictor of clear renal cell carcinoma T stage, Adipocyte 10 (1) (2021) 285–292.
[15] G. Wei, H. Sun, K. Dong, L. Hu, Q. Wang, Q. Zhuang, et al., The thermogenic activity of adjacent adipocytes fuels the progression of ccRCC and compromises anti-tumor therapeutic efficacy, Cell Metabol. 33 (10) (2021) 2021–2039, e2028.
[16] A. Sanchez, H. Furberg, F. Kuo, L. Vuong, Y. Ged, S. Patil, et al., Transcriptomic signatures related to the obesity paradox in patients with clear cell renal cell carcinoma: a cohort study, Lancet Oncol. 21 (2) (2020) 283–293.
[17] A.A. Hakimi, H. Furberg, E.C. Zabor, A. Jacobsen, N. Schultz, G. Ciriello, et al., An epidemiologic and genomic investigation into the obesity paradox in renal cell carcinoma, J. Natl. Cancer Inst. 105 (24) (2013) 1862–1870.
[18] A. Mahamid, I. Ashkenazi, M. Shapira-Rootman, O. Olsha, R. Alfici, E.Y. Bekhor, et al., Impact of increased visceral fat measured by CT on colon adenocarcinoma stage, J. Gastrointest. Cancer 48 (4) (2017) 347–352.
[19] J.P. Obeid, R. Stoyanova, D. Kwon, M. Patel, K. Padgett, J. Slingerland, et al., Multiparametric evaluation of preoperative MRI in early stage breast cancer: prognostic impact of peri-tumoral fat, Clin. Transl. Oncol. 19 (2) (2017) 211–218.
[20] A. Xia, Y. Chen, J. Chen, Y. Pan, L. Bao, X. Gao, Prognostic value of the albumin-to-alkaline phosphatase ratio on urologic outcomes in patients with non-metastatic renal cell carcinoma following curative nephrectomy, J. Cancer 10 (22) (2019) 5494–5503.
[21] M.T. Paris, H.F. Furberg, S. Petruzella, O. Akin, A.M. Hotker, M. Mourtzakis, Influence of contrast administration on computed tomography-based analysis of visceral adipose and skeletal muscle tissue in clear cell renal cell carcinoma, JPEN - J. Parenter. Enter. Nutr. 42 (7) (2018) 1148–1155.
[22] B.H. Eisner, J. Zargooshi, A.D. Berger, M.R. Cooperberg, S.M. Doyle, S. Sheth, et al., Gender differences in subcutaneous and perirenal fat distribution, Surg. Radiol. Anat. 32 (9) (2010) 879–882.
[23] A.J. Davidiuk, A.S. Parker, C.S. Thomas, B.C. Leibovich, E.P. Castle, M.G. Heckman, et al., Mayo adhesive probability score: an accurate image-based scoring system to predict adherent perinephric fat in partial nephrectomy, Eur. Urol. 66 (6) (2014) 1165–1171.
[24] L. Albiges, A.A. Hakimi, W. Xie, R.R. McKay, R. Simantov, X. Lin, et al., Body mass index and metastatic renal cell carcinoma: clinical and biological correlations, J. Clin. Oncol. 34 (30) (2016) 3655–3663.
[25] P. Penson, D.L. Long, G. Howard, V.J. Howard, S.R. Jones, S.S. Martin, et al., Associations between cardiovascular disease, cancer, and very low high-density lipoprotein cholesterol in the REasons for Geographical and Racial Differences in Stroke (REGARDS) study, Cardiovasc. Res. 115 (1) (2019) 204–212.
[26] F. Posch, J. Riedl, E.M. Reitter, M.J. Crowther, E. Grilz, P. Quehenberger, et al., Dynamic assessment of venous thromboembolism risk in patients with cancer by longitudinal D-Dimer analysis: a prospective study, J. Thromb. Haemostasis 18 (6) (2020) 1348–1356.

[27] A.P. Bernstein, E.B. Fram, A. Sankin, E. Kovac, A. Srivastava, J. DiVito, et al., A comparison of perinephric fat surface area and Mayo Adhesive Probability score in predicting malignancy in T1 renal masses, Urol. Oncol. 36 (11) (2018) 499.e417, 499e422.
[28] G. Guo, Y. Wang, Y. Zhou, Q. Quan, Y. Zhang, H. Wang, et al., Immune cell concentrations among the primary tumor microenvironment in colorectal cancer patients predicted by clinicopathologic characteristics and blood indexes, J Immunother Cancer 7 (1) (2019) 179.
[29] I. Lal, K. Dittus, C.E. Holmes, Platelets, coagulation and fibrinolysis in breast cancer progression, Breast Cancer Res. 15 (4) (2013) 207.
[30] M.M. Fuster, J.D. Esko, The sweet and sour of cancer: glycans as novel therapeutic targets, Nat. Rev. Cancer 5 (7) (2005) 526–542.
[31] C. Czoski-Murray, M. Lloyd Jones, C. McCabe, K. Claxton, Y. Oluboyede, J. Roberts, et al., What is the value of routinely testing full blood count, electrolytes and urea, and pulmonary function tests before elective surgery in patients with no apparent clinical indication and in subgroups of patients with common comorbidities: a systematic review of the clinical and cost-effective literature, Health Technol. Assess. 16 (50) (2012) 1–159, i-xvi.