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The prevalence and impact of overweight and hypertension among patients with pancreatic cancer

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Abstract

Introduction. Pancreatic cancer (PC) remains one of the most deadly malignancies with rising incidence. As therapeutical options seem unsatisfactory, great effort should be put into identifying and reducing risk factors as well as distinguishing possible factors influencing patient outcomes. The study aimed to describe the prevalence of overweight and hypertension among PC patients, analyse the possible association between overweight, hypertension and clinicopathological factors and distinguish variables influencing survival.

Material and methods. A retrospective analysis of medical records was performed. The study was designed in two branches: (1) the comparison of patients with hypertension (HTN group) and without; (2) the comparison of patients with BMI $\geq$ 25 and patients with BMI < 25. Statistical analysis with the usage of appropriate tests was conducted.

Results. No differences in survival between studied groups in the two branches were determined, even after subdividing into adjuvant and palliative types of treatment. Patients with HTN were more likely to be older, have diabetes and be diagnosed without distant metastases. BMI, ACEIs/ARBs use, diabetes, CRP/lymphocyte ratio (CLR) and AJCC IIb stage influenced survival. Patients with overweight/obesity were more likely to have an autoimmune disease, metastases in $\geq$ 4 lymph nodes (N2), tumour size between 2 and 4 cm (T2) and experience neutropenia as side effect of palliative chemotherapy. Higher BMI and CRP level influenced survival.

Conclusions. The exact effect of ACEIs/ARBs on cancerogenesis should be further studied. CLR appears to be a feasible marker for prognosis in PC.

Keywords: oncology, pancreatic cancer, hypertension, obesity

Introduction

Pancreatic cancer (PC) remains one of the most deadly malignancies with a rising incidence. According to the 2020 Global Cancer Observatory (GLOBOCAN) report, PC accounts for almost as many deaths as cases and is currently the seventh leading cause of cancer death [1]. The incidence is projected to increase, reflecting the increasing prevalence of PC key risk factors [2]. Non-hereditary risk factors for PC could be divided into modifiable and non-modifiable. Modifiable encompass tobacco smoking, excessive alcohol consumption, pancreatitis, obesity, type 2 diabetes mellitus (DM), and metabolic syndrome, while non-modifiable factors include male sex, older age, and ethnicity [3]. PC survival rates remain unsatisfactory, after having slightly improved over the past 30 years from < 5% to 9% for overall survival (OS). Low survival rates are primarily associated with advanced, surgically unresectable stages of disease at the time

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of diagnosis [4]. Other factors influencing survival include early distant metastases, resistance to conventional treatment schemes, and a highly desmoplastic tumor microenvironment. Pancreatic cancer treatment options remain limited, as no immunotherapeutic or anti-angiogenic regimens have been approved [5]. If possible, the current approach encompasses multidisciplinary treatment with surgery, chemotherapy, and chemoradiotherapy [6]. The two approved, most commonly used chemotherapy regimens are mFOLFIRINOX and gemcitabine with nab-paclitaxel. Despite aggressive chemotherapy, most patients eventually require palliative care and symptom management [7].

As therapeutical options seem unsatisfactory, great effort should be put into identifying and reducing risk factors and distinguishing possible factors influencing patient outcomes. The growing incidence points out metabolic syndrome and its components (insulin resistance, central obesity, hypertension, and features of atherogenic dyslipidemia) as some of the most significant risk factors [8, 9]. Due to population aging, it is estimated that the number of elderly PC patients will continue to rise [10]. The aging population is also associated with a higher prevalence of metabolic syndrome [11]. It seems crucial to focus on characterizing patients with PC concomitant with particular components of metabolic syndrome. More specific characterization might provide better patient care and impact further outcomes.

Our study aimed to describe the prevalence of overweight and hypertension among PC patients, analyze possible associations between overweight, hypertension, and clinicopathological factors, and distinguish variables influencing survival.

Material and methods

Patients, data collection, and study design

We retrospectively analyzed patients diagnosed with PC between 2012 and 2021 at the Central Clinical Hospital of the Ministry of Interior and Administration in Warsaw, Poland. Clinical data from patients were extracted from the hospital patient records. A total number of 175 patients was included in the study for analysis after excluding 52 patients with neuroendocrine tumors and 58 patients who received only one course of chemotherapy to reduce data variability and include information about adverse effects of chemotherapy. The study was designed in two branches:

1) comparison between patients with hypertension (HTN group) and patients without hypertension (non-HTN group);
2) comparison of patients with BMI $\geq$ 25 and patients with BMI < 25 (Fig. 1).

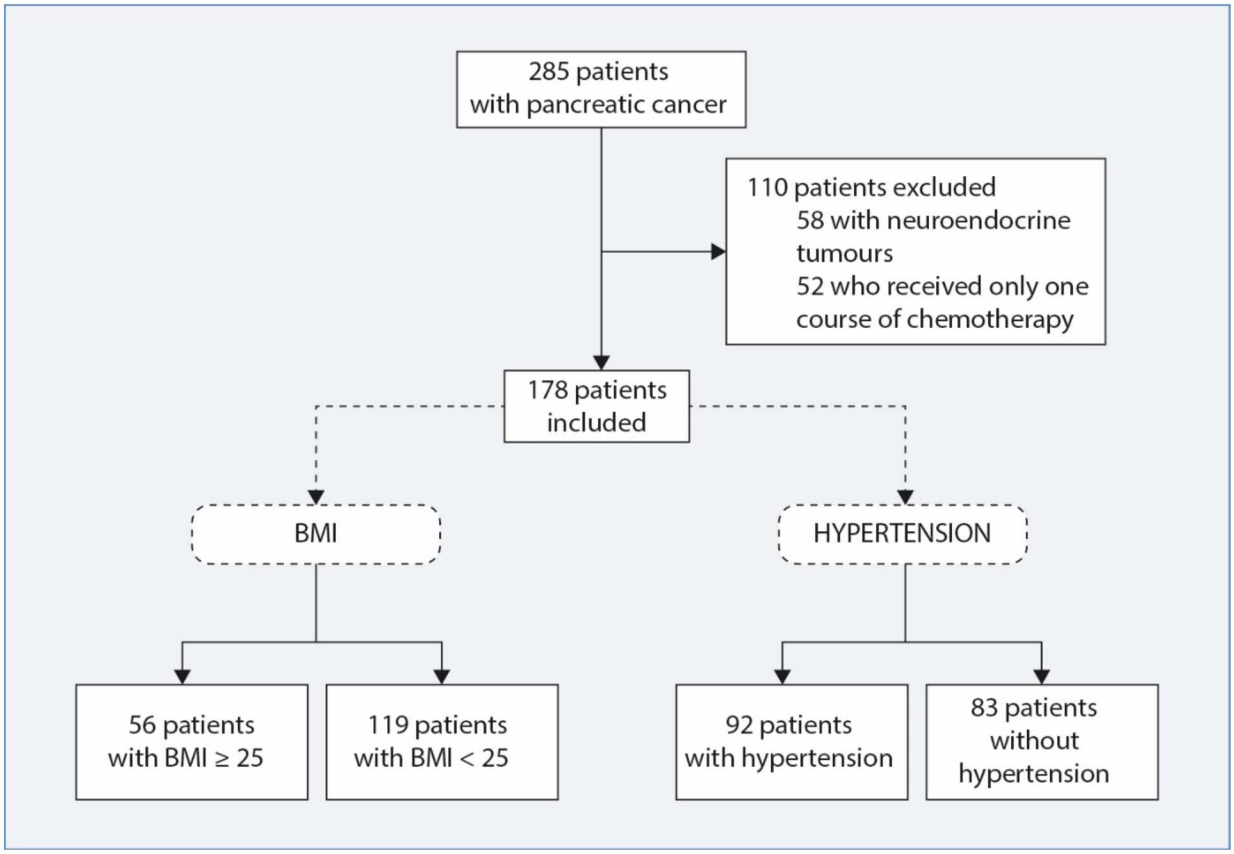

Figure 1. Summary of study design with exclusion criteria; BMI — body mass index

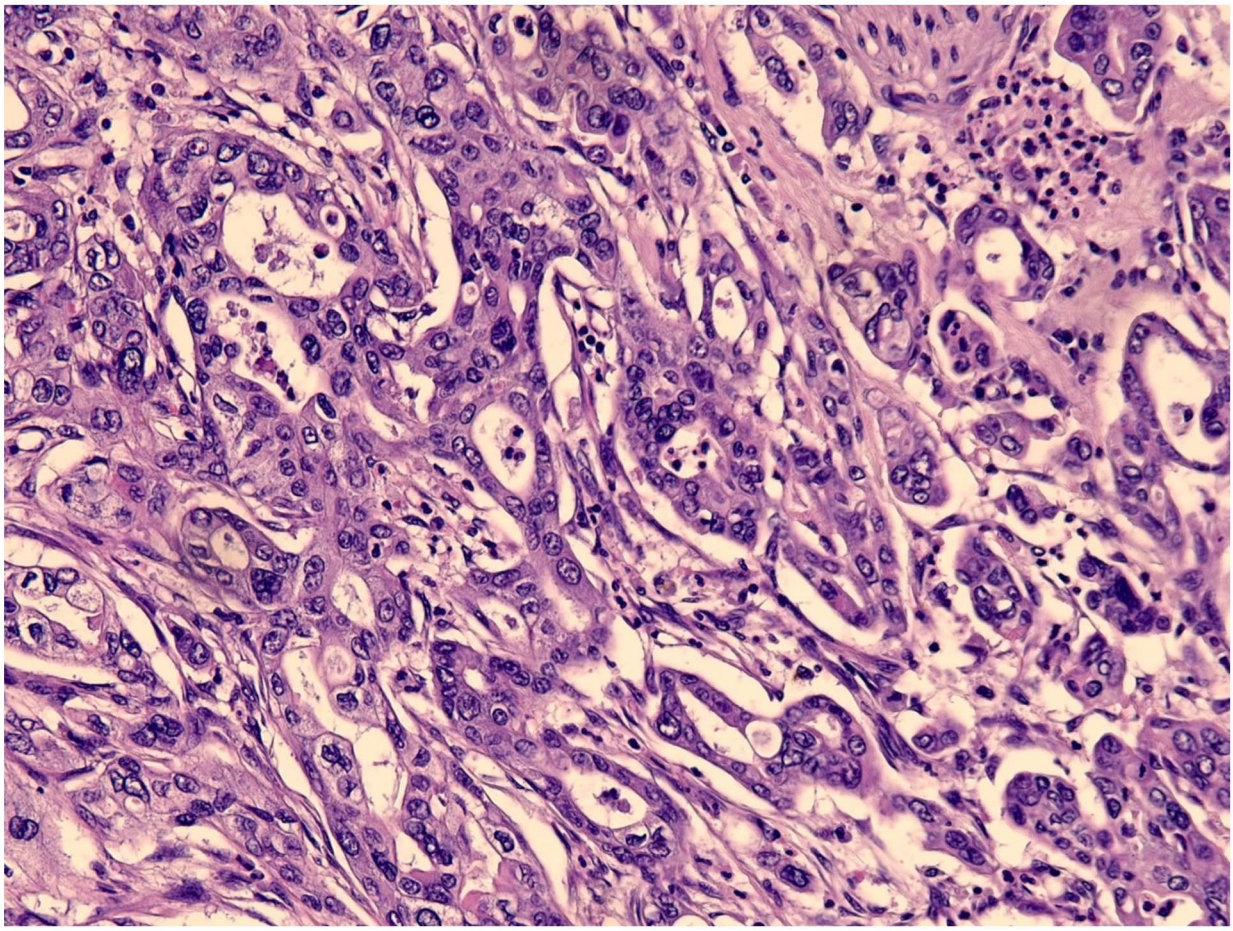

Figure 2. Histopathological image of pancreatic ductal adenocarcinoma (H&E, original magnification, 200×)

Analyzed data encompassed sex, age, weight, height, cigarette smoking, family history of cancers, history of other primary tumors, other diseases with described treatment methods, World Health Organization (WHO) performance status, pathological variables (tumor site, tumor size, histological grading, nodal involvement, tumor stage, resection margin) (Fig. 2), treatment data (type of the operation, vascular reconstruction, postoperative complications, adjuvant and palliative chemotherapy, ad side effects), laboratory findings before the first course of chemotherapy, survival, and progression time.

Body mass index (BMI) was calculated by dividing weight in kilograms (kg) by height in square meters (m). Data about weight and height were collected before the first course of chemotherapy.

Hypertension was defined based on one or more of the following criteria:

1) listed hypertension in patient history;
2) taking anti-hypertensive medication or
3) systolic blood pressure (SBP) in the clinic ≥ 140 mm Hg and/or diastolic blood pressure (DBP) ≥ 90 mm Hg following repeated examination.

In the analyses considering smoking, we took into account only active smoking. Laboratory findings were analyzed before chemotherapy. The C-reactive protein (CRP)/lymphocyte ratio (CLR) biomarker was additionally established. For statistical analysis, the cutoff value of 1.8 was confirmed based on the study by Fan et al. [12].

Diabetes mellitus was defined based on one or more of the following criteria:

1) diabetes listed in medical history;
2) two consecutive fasting glucose levels ≥ 140 mg/dL (7.8 mmol/L);
3) random plasma glucose ≥ 200 mg/dL (11.1 mmol/L) in patients with classic symptoms of hyperglycemia or hyperglycaemic crisis or
4) 2-hour plasma glucose ≥ 200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test.

The study did not include abnormal cholesterol and triglyceride levels, as they were not routinely analyzed before the first course of chemotherapy.

Tumor staging was performed according to the American Joint Cancer Committee (AJCC) Staging Manual, 8th edition. Recurrence was detected with abdominal and chest computed tomography (CT) during the follow-up period. The study's primary endpoint was defined as OS. OS was calculated from the date of the histologically verified diagnosis (biopsies or material from surgeries) to the date of the last follow-up or death. Deaths were identified by reviewing the medical records.

Statistical analysis

IBM SPSS 26 Statistics was used for statistical analysis. All analyzed variables were presented as means and standard deviations or frequencies with percentages. Estimation of mean differences between two independent groups was performed using the Mann-Whitney U test. Relationships between the two nominal variables were estimated using Pearson chi-squared or Fisher's exact test. Median OS was calculated using the Kaplan-Meier method, and differences were measured using the log-rank test, defined as the time from diagnosis until death (living patients were censored at the time of their last follow-up). Kaplan-Meier curves presented a summary of the data on survival probability. Univariate and multivariate analyses were conducted to examine the effect of single or multiple potential prognostic parameters on median OS. Cox regression models were presented as hazard ratios (HR) and were associated with a 95% confidence interval (CI). An alpha level of 0.05 was selected as statistically significant.

Ethical approval

The study was approved by the Bioethics Committee of the Medical University of Warsaw (AKBE/144/2022). The work was carried out following the Code of Ethics of the World Medical Association (Declaration of Helsinki) on medical research involving human subjects and the ethical principle defined in the Farmington Consensus 1997.

Results

Group with hypertension

Of 175 PC patients, 92 (52.6%) were also diagnosed with HTN. From medical data, 53 schemes of hypertensive treatment were retrieved. Most of the patients were treated with two anti-hypertensive drugs (37.5%), predominantly with the combination of angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers (ACEIs/ARBs) and β-blockers.

The majority of HTN patients were men (56.5%) with WHO performance status 1 (72.5%). The mean age was 66.3, with a range from 44 to 87. At the beginning of chemotherapy, the median BMI was 23.7 kg/m2, while 39.8% of patients were overweight or obese. Regarding medical history, 50.0% had DM, 12.0% autoimmune disease, 9.8% other primary tumors, and 21.0% family history of cancers. History of active smoking concerned 33.8% of patients.

Most patients in the studied group were diagnosed with PC in the head of the pancreas (77.2%) with 52.2% having grade 2 while the most prevalent AJCC cancer stage was IIB (36.1%). Neuroinvasion was confirmed in 80.0% of the analyzed samples, while angioinvasion in 74.5%. Regarding treatment, 72.8% of patients underwent surgery (74.6% — the Whipple procedure), predominantly without further complications. Eleven of the operated patients (16.4%) required vascular reconstruction. Sixty-one patients (91.1%) received adjuvant chemotherapy, primarily based on gemcitabine (73.8%), with neutropenia as the most common side effect (65.6%). Eight-seven percent of patients eventually received palliative treatment with gemcitabine and nab-paclitaxel as the most common scheme (40.0%). Adverse effects were developed by 63.75% of palliatively treated patients, among which neutropenia was the most common.

Statistical analysis comparing the HTN group with the non-HTN group is presented in Table 1. Hypertension patients were more likely to be older ($p < 0.001$), have DM ($p = 0.033$), and have no distant metastases at the time of diagnosis ($p = 0.005$).

In Kaplan–Meier analysis, no significant differences concerning OS, disease-free survival (DFS), and progression-free survival (PFS) were confirmed (Tab. 1. Fig. 3–5).

The analyzed group was further subdivided into a group receiving adjuvant chemotherapy and a group receiving palliative chemotherapy (patients who presented with advanced disease at the time of diagnosis). In general, patients treated with adjuvant chemotherapy turned out to have significantly higher median OS than patients with advanced disease (20 months *vs.* 14, $p < 0.00012$). Nevertheless, no difference in survival between non-HTN and HTN groups was detected.

In the univariate analysis for survival in the HTN group, higher BMI ($p = 0.002$), using ACEIs/ARBs ($p = 0.003$), DM diagnosis ($p = 0.003$), and CLR ≤ 1.8 ($p = 0.013$) were associated with longer survival. On the other hand, AJCC stage IIB ($p = 0.037$) was associated with shorter survival (Tab. 2).

Statistically significant prognostic factors were further analyzed in multivariate Cox regression using the backward method based on Wald statistics. ACEIs/ARBs use was the last excluded out of five studied prognostic factors, which means it was the strongest predictor of survival in the HTN group.

Table 1. Baseline characteristics of participants according to hypertension occurrence with statistical analysis

Variable	Non-HTN group Mean ± SD/n (%)/MD (95% CI)	HTN group Mean ± SD/n (%)/MD (95% CI)	p-value
Demography			
Gender (male)	35 (42.2%)	52 (56.5%)	0.070
Age [years]	60.95 ± 10.37	66.34 ± 8.33	**< 0.001**
Medical history			
WHO status (0/1/2/0–1/1–2/2–3)	3.7%/75.3%/16.0%/0.0%/3.7%/1.2%	7.7%/72.5%/14.3%/2.2%/3.3%/0.0%	0.517
BMI (≥ 25)	23 (32.4%)	33 (39.8%)	0.402
History of smoking	25 (39.1%)	27 (33.8%)	0.601
Autoimmune disease	9 (10.8%)	11 (12.0%)	1.000
Diabetes mellitus	28 (33.7%)	46 (50.0%)	**0.033**
History of other CA	7 (8.4%)	9 (9.8%)	0.799
Family history of CA	22 (34.3%)	17 (21.0%)	0.090
Number of relatives with CA	1.41 ± 0.67	1.35 ± 0.49	0.986
Histopathology			
Localisation of PC			0.220
Head	75.9%	77.2%	
Body	7.2%	7.6%	
Tail	8.4%	5.4%	
Head and body	3.6%	3.3%	
Body and tail	1.2%	6.5%	
Undetermined	3.6%	0.0%	
Grading (G1/G2/G3/Gx)	12.0%/50.6%/13.3%/24.1%	10.9%/52.2%/16.3%/20.7%	0.901
T (T1/T2/T3/T4/Tx)	2.4%/14.5%/50.6%/4.8%/27.7%	1.1%/19.6%/46.7%/3.3%/29.3%	0.818
N (N0/N1/N2/Nx)	13.3%/39.8%/18.1%/28.9%	20.7%/38.0%/13.0%/28.3%	0.542
M (M0/M1)	50.6%/49.4%	71.7%/28.3%	**0.005**
AJCC cancer stage (IA/IB/IIA/IIB/III/IV)	1.3%/1.3%/5.0%/28.7%/13.8%/50.0%	1.2%/9.6%/8.4%/36.1%/13.3%/31.3%	0.072
R (R0/R1/R2/None)	32.5%/32.5%/2.4%/32.5%	44.6%/28.3%/0.0%/27.2%	0.210
Neuroinvasion	38 (86.4%)	40 (80.0%)	0.583
Angioinvasion	37 (82.2%)	38 (74.5%)	0.460
Treatment			
Adverse effects — adjuvant chemotherapy	28 (71.8%)	51 (83.6%)	0.209
Neuropathy	2 (5.1%)	4 (6.6%)	1.000
Neutropenia	22 (56.4%)	40 (65.6%)	0.402
Hepatological	3 (7.7%)	3 (4.9%)	0.676
Adverse effects — palliative chemotherapy	57 (80.3%)	51 (77.3%)	0.682
Neutropenia	33 (46.5%)	33 (50.0%)	0.734
Hepatological	7 (9.9%)	4 (6.1%)	0.535
Neuropathy	12 (16.9%)	9 (13.6%)	0.642
Operative complications	3 (5.3%)	5 (7.4%)	0.726
Laboratory findings			
CEA ≥ 5 ng/mL	20 (37.7%)	21 (31.8%)	0.562
CA19-9 ≥ 37 IU/mL	44 (62.0%)	45 (53.6%)	0.330
CLR > 1.8	26 (57.8%)	32 (57.1%)	1.000
LYM 1 × 10^3/ µL	2.13 ± 2.28	2.88 ± 6.00	0.289
HGB [g/dL]	12.34 ± 1.45	12.54 ± 1.58	0.407
Plt 1 × 10^3/ µL	297.71 ± 158.85	290.12 ± 114.80	0.717
CRP [mg/L]	30.38 ± 61.82	14.57 ± 22.98	0.110
Survival			
OS	19.00 (15.89–22.11)	20.00 (15.42–24.58)	0.255
DFS	13.00 (6.22–19.78)	12.00 (9.42–14.58)	0.809
PFS	5.00 (4.13–5.87)	7.00 (5.15–8.86)	0.951

Bolded p-value — value statistically significant; AJCC — The American Joint Committee on Cancer; BMI — body mass index; CA — cancer; CA19-9 — carbohydrate antigen 19-9; CEA — carcinoembryonic antigen; CI — confidence interval; CLR — C-reactive protein/lymphocytes ratio; CRP — C-reactive protein; DFS — disease-free survival; HGB — haemoglobin; HTN — hypertension; LYM — lymphocytes; M — distant metastases; MD — median; N — nodal involvement; n — number; OS — overall survival; PC — pancreatic cancer; PFS — progression-free survival; PLT — platelets; R — resection margin; SD — standard deviation; T — tumour size; WHO status — World Health Organization performance status

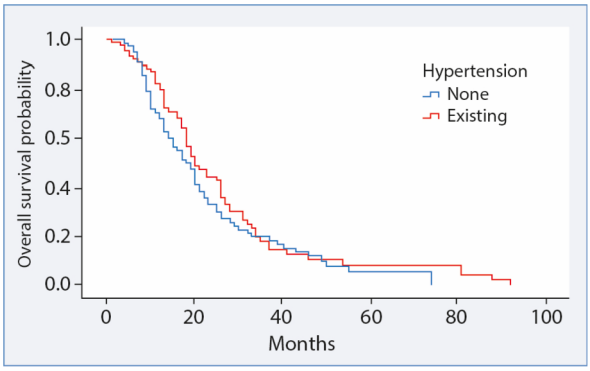

Figure 3. Overall survival of pancreatic cancer patients in the hypertension (HTN) and non-HTN groups

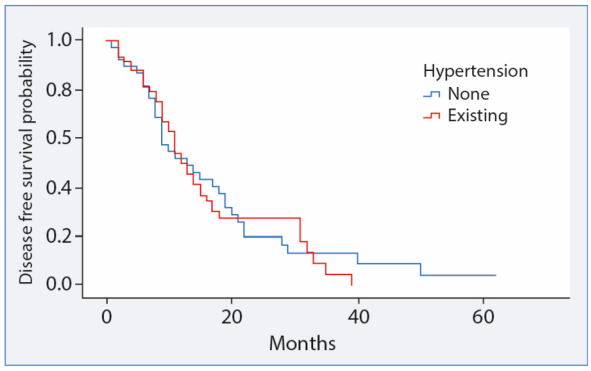

Figure 4. Disease-free survival of pancreatic cancer patients in the hypertension (HTN) and non-HTN groups

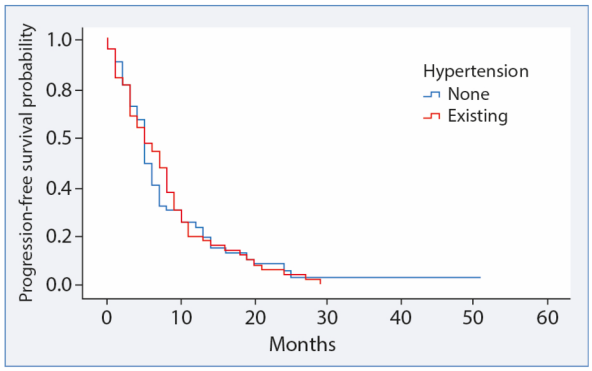

Figure 5. Progression-free survival of pancreatic cancer patients in the hypertension (HTN) and non-HTN groups

Group with BMI ≥ 25

Of 175 PC patients, 56 (32.0%) were overweight or obese. Most were men (51.8%) with WHO performance status 1 (78.6%). The mean age was 62.7, with a range from 40 to 82. At the beginning of chemotherapy, the median BMI was 27.8 kg/m^2, with a mean of 28.5 kg/m^2 [standard deviation (SD) = 3.0, range 25.0–36.2].

Table 2. Univariate analysis of survival in the hypertension (HTN) group

Variable	HR (95% CI)	p-value
Age	1.014 (0.984–1.045)	0.358
WHO performance status		
0	Ref	–
1	0.192 (0.035–1.057)	0.058
2	0.399 (0.093–1.707)	0.215
0/1	0.264 (0.054–1.294)	0.100
1/2	0.516 (0.046–5.841)	0.593
BMI ≥ 25		
No	Ref	–
Yes	0.384 (0.211–0.670)	**0.002**
History of smoking		
No	Ref	–
Yes	1.294 (0.742–2.258)	0.364
Diabetes mellitus		
No	Ref	–
Yes	0.399 (0.219–0.727)	**0.003**
Family history of CA		
No	Ref	–
Yes	0.674 (0.355–1.278)	0.227
History of other CA		
No	Ref	–
Yes	0.565 (0.265–1.205)	0.139
Number of anti-hypertensive drugs		
1	Ref	–
2	0.582 (0.075–4.541)	0.606
3	0.521 (0.066–4.118)	0.536
4	0.579 (0.072–4.628)	0.606
5	0.150 (0.013–1.767)	0.132
ACEIs/ARBs usage		
No	Ref	–
Yes	0.170 (0.054–0.538)	**0.003**
B-blockers usage		
No	Ref	–
Yes	0.848 (0.414–1.738)	0.653
CCBs usage		
No	Ref	–
Yes	1.137 (0.573–2.257)	0.713
Diuretics usage		
No	Ref	–
Yes	0.744 (0.379–1.46)	0.390
α-blockers usage		
No	Ref	–
Yes	1.806 (0.636–5.131)	0.267
AJCC cancer stage		
IB	Ref	–
IIA	0.656 (0.247–1.741)	0.398
IIB	2.035 (1.045–3.961)	**0.037**
III	0.562 (0.312–1.0132)	0.055
IV	0.792 (0.337–1.865)	0.594

→

Table 2 cont. Univariate analysis of survival in the hypertension (HTN) group

Variable	HR (95% CI)	p-value
Adverse effects — adjuvant chth		
No	Ref	–
Yes	1.003 (0.552–1.823)	0.993
Neutropenia		
No	Ref	–
Yes	0.763 (0.438–1.328)	0.339
Adverse effects — palliative chth		
No	Ref	–
Yes	0.968 (0.541–1.732)	0.913
Neutropenia		
No	Ref	–
Yes	1.625 (0.966–2.734)	0.067
CLR > 1.8		
No	Ref	–
Yes	1.886 (1.143–3.111)	**0.013**
LYM 1 × 10^3/ µL		
≤ 1	Ref	–
> 1	0.839 (0.356–1.977)	0.688
CRP [mg/L]		
≤ 5	Ref	–
> 5	1.361 (0.807–2.297)	0.247

Bolded p-value — value statistically significant; ACEIs — angiotensin-converting enzyme inhibitors; AJCC — The American Joint Committee on Cancer; ARBs — angiotensin II receptor blockers; BMI — body mass index; CA — cancer; CCBs — calcium channel blockers; chth — chemotherapy; CI — confidence interval; CLR — C-reactive protein/lymphocytes ratio; CRP — C-reactive protein; HR — hazard ratio; LYM — lymphocytes; Ref — reference

Regarding medical history, 58.9% of patients had HTN, 50.0% DM, 21.4% autoimmune disease, 7.14% other primary tumors, and 18.5% family history of cancers. History of active smoking concerned 30.2%.

Most patients in the studied group were diagnosed with PC in the head of the pancreas (78.6%) with 51.8% having grade 2 while the most prevalent AJCC cancer stage was IIB (21.6%). Neuroinvasion was confirmed in 93.5% of the analyzed samples while angioinvasion in 87.9%. Regarding treatment, 66.1% of patients underwent surgery (83.8% — the Whipple procedure), predominantly without further complications. Four of the operated patients (10.8%) required vascular reconstruction. Thirty-two (86.5%) received adjuvant chemotherapy, primarily based on gemcitabine (68.8%). Twenty-five suffered from adverse effects, predominantly neutropenia (76.0%). In total, 78.6% of patients eventually received palliative treatment, primarily based on gemcitabine with nab-paclitaxel (65.9%). Adverse effects were developed by 86.4% of palliatively treated patients, among which neutropenia was the most common.

Statistical analysis comparing groups with BMI < 25 and BMI ≥ 25 is presented in Table 3. Patients with overweight or obesity were more likely to have an autoimmune disease (p = 0.020), metastases in 4 or more lymph nodes (N2) (p = 0.041), tumor size between 2 and 4 cm (T2) (p = 0.022); they were more likely to experience neutropenia as a side effect of palliative chemotherapy (p = 0.014).

In Kaplan-Meier analysis, no significant differences concerning OS, DFS, and PFS were confirmed, even after subdividing into adjuvant and palliative types of treatment (Tab. 3, Fig. 6–8).

In the univariate analysis for survival in the studied group, higher BMI (p = 0.021) was associated with longer survival, whilst a CRP level higher than 5 mg/L (p = 0.025) with shorter survival (Tab. 4). In the further multivariate analysis, BMI was confirmed as the strongest predictor of survival.

Discussion

Worldwide, HTN is the leading modifiable risk factor for premature deaths. The prevalence and absolute burden of HTN have increased over the past few years [13]. Approximately 60% of the population is diagnosed with HTN by the age of 60 years, and about 65% of men and 75% of women develop high blood pressure by 70. As the incidence of PC is also rising with age — 80% of the cases are diagnosed in people between 60 and 80 years of age, HTN is prevalent in this group [14]. In our study, over half of the analyzed group was diagnosed with HTN (52.6%), and the group with HTN was significantly older than the group without HTN (p < 0.001). In our previous analysis, DM was confirmed to be prevalent in PC patients [15]. Our results were in agreement with earlier studies, in which the prevalence of DM in PC patients was estimated to reach 40–65% [16]. In the current analysis, HTN patients were more likely to be diagnosed with DM (p = 0.033). Moreover, DM diagnosis was confirmed to be a prognostic factor for longer survival (p = 0.003). Reports regarding the impact of co-incidence of DM and PC on survival are ambiguous. Studies suggesting improved survival in DM patients discuss the positive effect of metformin on survival through various anti-cancer mechanisms [17, 18].

Drug therapy for HTN is recommended to come from one of four drug classes — calcium channel blockers (CCBs), thiazide diuretics, and ACEIs/ARBs. Two-drug treatment should be initiated in patients with blood pressure over 20/10 mmHg above the target [19]. In the studied group, most patients were treated with a two-drug combination, most with a combination of ACEIs/ARBS and β-blockers. In the univariate analysis, using ACEIs/ARBs was associated with longer survival (p = 0.003). In the

Table 3. Baseline characteristics of participants according to body mass index (BMI) with statistical analysis

Variable	BMI < 25 Mean ± SD/n (%)/MD (95% CI)	BMI ≥ 25 Mean ± SD/n (%)/ MD (95% CI)	p-value
Demography			
Sex (male)	47 (48.0%)	29 (51.8%)	0.738
Age [years]	64.88 ± 9.82	62.68 ± 8.48	0.069
Medical history			
WHO status (0/1/2/01/1–2)	4.2%/75.8%/15.8%/0.0%/4.2%	5.4%/78.6%/14.3%/1.8%/0.0%	0.374
History of smoking	35 (40.2%)	16 (30.2%)	0.279
Hypertension	50 (51.0%)	33 (58.9%)	0.402
Autoimmune disease	7 (7.1%)	12 (21.4%)	**0.020**
Diabetes mellitus	35 (35.7%)	28 (50.0%)	0.091
History of other CA	11 (11.2%)	4 (7.1%)	0.574
Family history of CA	28 (32.2%)	10 (18.5%)	0.083
Number of relatives with CA	1.46 ± 0.64	1.10 ± 0.31	0.087
Histopathology			
Localisation of PC			0.896
Head	79.6%	78.6%	
Body	7.1%	8.9%	
Tail	5.1%	5.4%	
Head and body	5.1%	1.8%	
Body and tail	2.0%	3.6%	
Undetermined	1.0%	1.8%	
Grading (G1/G2/G3/Gx)	13.3%/49.0%/14.3%/23.5%	12.5%/51.8%/14.3%/21.4%	0.987
T (T1/T2/T3/T4/Tx)	2.0%/13.3%/57.1%/5.1%/22.4%	0.0%/28.6%/33.9%/3.6%/33.9%	**0.022**
N (N0/N1/N2/Nx)	18.4%/45.9%/13.3%/22.4%	14.3%/26.8%/25.0%/33.9%	**0.041**
M (M0/M1)	64.3%/35.7%	58.9%/41.1%	0.604
AJCC cancer stage (IA/IB/IIA/IIB/III/IV)	1.1%/4.3%/7.7%/37.6%/12.9%/36.6%	0.0%/7.8%/5.9%/21.6%/19.6%/45.1%	0.341
R (R0/R1/R2/None)	45.9%/29.6%/0.0%/24.5%	30.4%/35.7%/0.0%/33.9%	0.157
Neuroinvasion	44 (78.6%)	29 (93.5%)	0.125
Angioinvasion	44 (75.9%)	29 (87.9%)	0.273
Treatment			
Adverse effects — adjuvant chemotherapy	49 (84.5%)	25 (78.1%)	0.566
Neuropathy	3 (5.2%)	2 (6.3%)	1.000
Neutropenia	40 (69.0%)	19 (59.4%)	0.366
Hepatological	5 (8.6%)	1 (3.1%)	0.416
Adverse effects — palliative chemotherapy	56 (73.7%)	38 (86.4%)	0.115
Neutropenia	30 (39.5%)	28 (63.6%)	**0.014**
Hepatological	7 (9.2%)	4 (9.1%)	1.000
Neuropathy	14 (18.4%)	6 (13.6%)	0.615
Operative complications	5 (6.6%)	3 (8.1%)	0.715
Laboratory findings			
CEA ≥ 5 ng/mL	22 (34.9%)	13 (32.5%)	0.834
CA19-9 ≥ 37 IU/mL	50 (55.6%)	30 (60.0%)	0.722
CLR > 1.8	34 (54.0%)	18 (60.0%)	0.658
LYM 1 × 10^3/ µL	3.09 ± 6.14	1.83 ± 0.69	0.707
HGB g/dL	12.29 ± 1.71	12.69 ± 1.22	0.161
PLT 1 × 10^3/ µL	312.27 ± 150.45	267.64 ± 106.16	0.142
CRP [mg/L]	18.16 ± 41.80	23.26 ± 51.16	0.308
Survival			
OS	18.00 (15.27–20.73)	22.00 (17.28–26.72)	0.352
DFS	13.00 (9.17–16.83)	14.00 (5.83–22.17)	0.757
PFS	6.00 (4.62–7.38)	7.00 (4.94–9.08)	0.523

Bolded p-value — value statistically significant; AJCC — The American Joint Committee on Cancer; CA — cancer; CA19-9 — carbohydrate antigen 19-9; CEA — carcinoembryonic antigen; CI — confidence interval; CLR — C-reactive protein/lymphocytes ratio; CRP — C-reactive protein; DFS — disease-free survival; HGB — haemoglobin; LYM — lymphocytes; M — distant metastases; MD — median; N — nodal involvement; n — number; OS — overall survival; PC — pancreatic cancer; PFS — progression-free survival; PLT — platelets; R — resection margin; SD — standard deviation; T — tumour size; WHO status — World Health Organization performance status

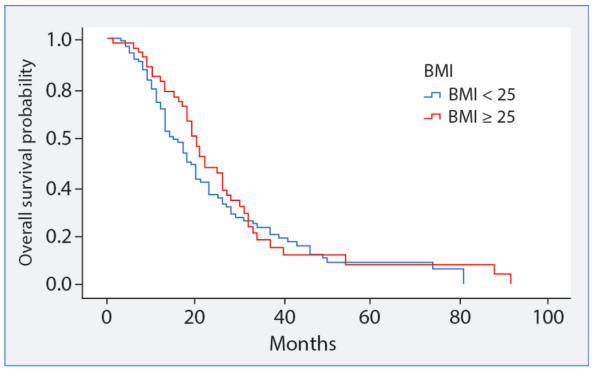

Figure 6. Overall survival of pancreatic cancer patients with body mass index (BMI) < 25 and BMI ≥ 25

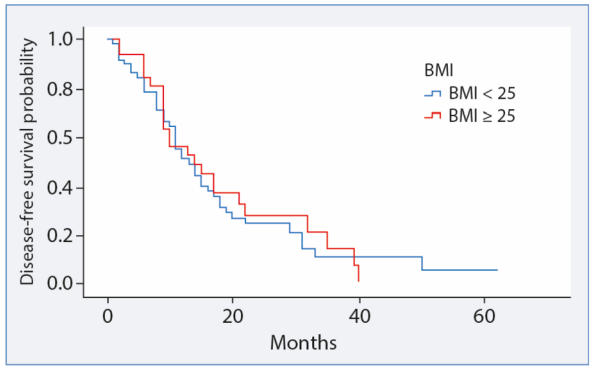

Figure 7. Disease-free survival of pancreatic cancer patients with body mass index (BMI) < 25 and BMI ≥ 25

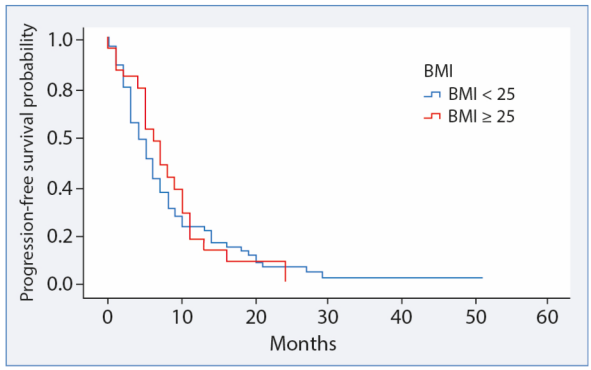

Figure 8. Progression-free survival of pancreatic cancer patients with body mass index (BMI) < 25 and BMI ≥ 25

subsequent multivariate Cox regression analysis using the backward method, it was the strongest predictor of survival in the HTN group. Similar to our analysis, in the study by Nakai et al. (2010) [20], the use of ACEIs/ARBs was associated with longer PFS and OS in patients with advanced PC receiving gemcitabine in monotherapy. Results from large population studies also imply that exposure to either ARBs or ACEI after PC diagnosis is significantly associated with improved survival [21]. Up-to-date

Table 4. Univariate analysis of survival in group with body mass index (BMI) ≥ 25

Variable	HR (95% CI)	p-value
Age	0.981 (0.943–1.020)	0.330
WHO performance status		
0	Ref	–
1	0.086 (0.005–1.531)	0.095
2	0.674 (0.091–5.017)	0.700
0/1	0.556 (0.064–4.815)	0.594
BMI	0.853 (0.745–0.976)	**0.021**
History of smoking		
No	Ref	–
Yes	0.696 (0.348–1.390)	0.304
Hypertension		
No	Ref	–
Yes	1.383 (0.740–2.584)	0.310
Diabetes Mellitus		
No	Ref	–
Yes	1.202 (0.643–2.248)	0.564
Autoimmune disease		
No	Ref	–
Yes	0.964 (0.228–4.093)	0.961
Family history of CA		
No	Ref	–
Yes	0.751 (0.331–1.704)	0.494
AJCC cancer stage		
IB	Ref	–
IIA	0.528 (0.121–2.306)	0.396
IIB	0.479 (0.130–1.757)	0.267
III	0.591 (0.238–1.464)	0.255
IV	1.005 (0.430–2.349)	0.991
Tumour localisation		
Head	Ref	–
Body	0.919 (0.214–3.945)	0.909
Tail	0.753 (0.144–3.931)	0.737
Head and body	7.137 (0.563–90.463)	0.129
Body and tail	7.137 (0.563–90.463)	0.129
Adverse effects — adjuvant chth		
No	Ref	–
Yes	0.890 (0.440–1.837)	0.771
Neutropenia		
No	Ref	–
Yes	1.060 (0.557–2.018)	0.860
Adverse effects — palliative chth		
No	Ref	–
Yes	1.250 (0.646–2.419)	0.507
Neutropenia		
No	Ref	–
Yes	1.426 (0.770–2.644)	0.259
CLR > 1.8		
No	Ref	–
Yes	0.546 (0.275–1.087)	0.085
LYM 1 × 10^3/ µL		
≤ 1	Ref	–
> 1	0.58 (0.174–1.934)	0.375
CRP [mg/L]		
≤ 5	Ref	–
> 5	1.447 (1.221–1.903)	**0.025**

Bolded p-value – value statistically significant; AJCC — The American Joint Committee on Cancer; CA — cancer; chth — chemotherapy; CI — confidence interval; CLR — C-reactive protein/lymphocytes ratio; CRP — C-reactive protein; HR — hazard ratio; LYM — lymphocytes; Ref — reference

preclinical and clinical studies support the role of the renin-angiotensin system (RAS) in regulating tumor growth and metastasis in different neoplasms, encompassing PC [22]. In the pancreas, RAS components are considered to mediate growth and further lead to carcinogenesis [23]. Angiotensin II has two receptors prevalent in human tissue — the angiotensin II type 1 (AT1) and the angiotensin II type 2 (AT2). Stimulation of the AT1 receptor is associated with increased cell proliferation, growth, and reduced apoptosis. ACEIs inhibit angiotensin II systemic formation and its downstream effects through receptors. ARBs were designed to displace angiotensin II from the AT1 receptor [24]. Initial studies identified angiotensin II as a potent mediator of vascular endothelial growth factor (VEGF) expression in PC cells through an AT1-dependent pathway. The inhibition of its receptor by ARBs may inhibit tumor growth via suppression of VEGF-mediated angiogenesis [21]. One of ARBs, telmisartan, turned out to inhibit PC cell proliferation by inducing cell cycle arrest [25]. On the other hand, another ARB, losartan, reduced stromal collagen and hyaluronan production in PC models and, as a result, increased vascular perfusion and drug delivery [5]. Currently, losartan is under investigation in several PC clinical trials, including the combination of losartan with mFOLFIRINOX and beam proton radiation or the combination of losartan with gemcitabine (NCT01821729, NCT01276613). Moreover, a phase II clinical study on the efficacy of irbesartan with gemcitabine/nab-paclitaxel treatment for patients with advanced PC is designed, as in preclinical studies, irbesartan was proved to inhibit chemotherapy resistance and consequently improve the therapeutic efficacy in PC patients [26].

Our analysis did not present associations between CCBs, diuretics, or β-blocker use, and patient survival. Various studies analyzing the effect of anti-hypertensive treatment on PC patient survival demonstrate contradictory results. A meta-analysis by Jiang et al. (2022) [27] confirmed that the use of anti-hypertensive medication (ACEIs/ARBs, CCBs, diuretics, β-blockers) does not have a negative effect on overall survival of PC patients; thus, they should continue to use these drugs to prevent cardiovascular events. Yang et al. (2021) [28] suggested that β-blockers usage before PC diagnosis is not correlated with survival advantage; nevertheless, continuous use before and after diagnosis presented survival benefits. The mechanism remains unclear, and the authors noted the need for further prospective studies [28]. Previous analysis conducted by Udumyan et al. (2017) [29] revealed that patients using β-blockers had lower cancer-specific mortality rates, especially users with higher daily doses and localized disease at diagnosis. In a retrospective cohort study, the authors concluded that CCBs may prolong survival in PC patients [30]. Principe et al. (2022) [31] used CCBs, such as amlodipine, which inhibited pro-survival extracellular signal-regulated kinase (ERK) signaling *in vitro* and remarkably enhanced therapeutic responses to gemcitabine in both orthotopic xenografts and transgenic PC models. Further prospective studies are required to establish the exact impact of anti-hypertensive treatment on PC patient survival.

Although in our analysis, patients in the HTN group were significantly more likely to be diagnosed without distant metastases ($p = 0.005$), no impact of HTN on progression or survival was observed, even after further subdividing patients into receiving adjuvant or palliative therapy. Patients with comorbidities, such as hypertension, might be suspected to experience shorter survival or time to progression; nevertheless, in our study, this observation failed to achieve statistical significance. This phenomenon might be associated with receiving holistic care from doctors with both internal medicine and oncology specialties. Moreover, being hospitalized in a multi-specialist center provides patients with integrated care by multidisciplinary teams. Multidisciplinary teams might become an effective tool to facilitate collaboration between different professionals and further improve outcomes of patients with comorbidities. Similar to our study, in a single-center analysis of 2323 PC patients, HTN did not correlate with OS and showed no statistical significance in univariate analyses [32]. The study by Iede et al. (2022) [33] showed that median OS in the HTN group was significantly longer than in the non-HTN group; nevertheless, the multivariate analysis failed to identify the usage of anti-hypertensive drugs as an independent prognostic factor for OS in PC patients.

The CLR level reflects the equilibrium state between the systemic inflammatory and immunological response. An elevated CLR indicates a decrease in immune response and an increase in systemic inflammation [34]. It seems unclear if the CLR could serve as a prognostic marker in PC. In our previous analysis, higher CLR and CRP levels were significantly associated with poorer OS in PC and DM patients. In the current study, a higher CLR was also associated with shorter survival in the HTN group ($p = 0.013$). Similar results were obtained in the study by Fan et al. (2020) [12] in which a CLR > 1.8 was correlated with poorer survival of PC patients, both in univariate and multivariate analysis. On the other hand, in the group with BMI $\geq$ 25 analyzed in our study, the CLR failed to reach statistical significance as a prognostic marker; nevertheless, a higher CRP level was associated with shorter survival in this group. In the study by Yuan et al. (2021) [35], pre-diagnostic lev-

els of CRP were associated with reduced survival in PC patients, demonstrating that chronic inflammation is a significant risk factor for PC and influences further survival. A Mendelian randomization analysis confirmed the causal mechanism in which obesity induces chronic inflammation and contributes to PC development [36]. Moreover, an increase in CRP levels during chemotherapy with the mFOLFIRINOX regimen positively correlated with disease progression [37].

On the one hand, obesity is a well-known modifiable risk factor for PC; on the other hand, several studies confirmed that a higher BMI was correlated with longer survival in PC patients [32, 38–40]. These findings concur with our results, in which a higher BMI was also associated with longer survival in the group with HTN and the group with overweight/obesity. In the further multivariate analysis of the group with BMI $\geq$ 25, a higher BMI was the strongest predictor of survival. Interestingly, many previous studies have reported that a BMI higher than 25 kg/m^2 is associated with improved survival in other malignancies. This phenomenon was described as the "obesity paradox" [41]. Scientists trying to explain the obesity paradox underlie that measurement of obesity with BMI presents some limitations and cannot reflect metabolic and endocrine disruption [42]. Also, in some cancers, unintentional weight loss may occur before diagnosis; thus, weight at the time of diagnosis may be misleading [43]. On the other hand, it has been suggested that lack of cachexia in obese patients with advanced cancers may underlie this paradox [44]. Cachexia is a multifactorial syndrome defined by non-volitional weight loss, sarcopenia, anorexia, fatigue, weakness, loss of appetite, taste alterations, and early satiety [45]. It has been shown to affect approximately 50% of oncological patients and be driven by reduced food intake and specific alterations in metabolism caused by host-tumor interactions [46]. Insufficient food intake is a significant driver of weight loss, while metabolic changes and reduced activity contribute to the loss of muscle mass, called sarcopenia [47]. PC is associated with the highest frequency of developing cancer cachexia-sarcopenia syndrome, negatively influencing tolerance and response to treatment and survival [40]. In this context, obesity might correlate with better survival; however, rigorous and prospective studies are necessary to define the impact of obesity in the oncology setting.

This study had several limitations. It was a single-center study, and the juxtaposition of results collected in other clinical centers would have ensured a more reliable analysis. Moreover, we could not eliminate potential selection bias due to the retrospective character of the research. The outpatient medical records did not indicate the change in patients' weight both before diagnosis and during treatment. No data about exact blood pressure measurements was collected. Nonetheless, we firmly believe that our outcomes provide new insight into the relationship between being overweight, hypertension, and PC.

Conclusions

Although hypertension and overweight are prevalent in PC patients, they seem to have no impact on outcomes. In the studied groups, we managed to distinguish some variables influencing survival. The exact effect of ACEIs/ARBs on cancerogenesis should be further investigated. The CLR seems to be a feasible marker of prognosis in PC.

Article Information and Declarations

Data availability statement

Correspondence and material requests should be addressed to M.F., A.B.K. or A.D.

Ethics statement

The study was acknowledged by the Bioethics Committee of the Medical University of Warsaw (AKBE/144/2022). The work was carried out following the Code of Ethics of the World Medical Association (Declaration of Helsinki) on medical research involving human subjects, the ethical principle defined in the Farmington Consensus 1997.

Author contributions

M.F.: conceptualization, data curation, investigation, writing — original draft, writing — review and editing; I.C.: writing — original draft; A.B.-K.: conceptualization, investigation, supervision, validation, writing — original draft, writing — review and editing; A.D.: conceptualization, data curation, investigation, supervision, validation, writing — original draft, writing — review and editing.

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Conflict of interest

The authors declare no conflict of interest.

Supplementary material

None.

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