MEANDROS MEDICAL AND DENTAL JOURNAL
March 2025 (1):101-107

Meandros Medical and Dental Journal
doi: 10.69601/meandrosmdj.1594499

Research Article

FACTORS AFFECTING ARTERIAL STIFFNESS LEVEL IN CANCER PATIENTS RECEIVING IMMUNOTHERAPY

Emine Esra Güner Yıldırım [1], Merve Bıyıklı Alemdar [2], Bilgin Demir [2], Merve Turan [2], Esin Oktay [2]*

[1] Department of Internal Medicine, Ataturk State Hospital, Aydın, Turkey
[2] Department of Medical Oncology, Adnan Menderes University Faculty of Medicine, Aydın, Turkey

*Correspondence: esinct@gmail.com

Received: *01 December 2024*
Revised: *08 January 2025*
Accepted: *15 January 2025*
Published: *20 March 2025*

ABSTRACT

Objective: This study aimed to investigate the factors affecting arterial stiffness in cancer patients receiving immunotherapy.

Materials and Methods: The height, weight, body mass index (BMI), age, sex, type of cancer, previous cancer treatment, agents used in the treatment, current immunotherapy agents, comorbid conditions, smoking history of 42 patients diagnosed with renal cell carcinoma (RCC), lung cancer, malignant melanoma and receiving immunotherapy treatment were recorded at the time of their first application and their arterial stiffness levels were measured. Following the first measurement, the patients were observed again in the third and sixth therapy cycles and their measurements were repeated and recorded. Factors affecting the arterial stiffness level of the patients were evaluated.

Results: Pulse wave velocity (PWV) increased with increased age ($p<0.01$). No significant difference was found between cancer type and PWV; however, patients with lung cancer had higher pulse pressure at the first measurement than other patients. No significant difference was found between immunotherapy agents and PWV. The PWV was found to be significantly higher in patients those with concomitant diseases ($p<0.005$). Pulse pressure was found to be higher in smokers than in non-smokers ($p<0.007$).

Conclusion: Smoking, sex and cancer type were effective in changing of pulse pressure in cancer patients receiving immunotherapy, and there was no significant difference in other factors; PWV increased with age; and that PWV was higher in those with additional diseases.

Keywords: Arterial stiffness, immunotherapy, cancer.

MEANDROS MEDICAL AND DENTAL JOURNAL
March 2025 (1):101-107
Meandros Medical and Dental Journal
doi: 10.69601/meandrosmdj.1594499

INTRODUCTION

Immunotherapy has become the standard treatment for cancer in recent years. Immunotherapies aim to prevent tumor cells from escaping the immune system by activating inhibitory signals at the immune control points of tumor cells (1). Especially renal cell carcinoma (RCC), malignant melanoma, head and neck cancers and lung cancer are cancers that benefit the most from immunotherapy treatment (2).

Cardiovascular disease (CVD) is a cause of mortality and morbidity in humans. Since cardiovascular events are significantly seen in people without risk factors, studies have been conducted to find various factors that can detect the development of atherosclerosis at an early stage, independent of known risk factors. Thus, has the concept of arterial stiffness emerged to assess the integrity of the arterial structure (3).

The patient's age, hypertension (HT), smoking, dyslipidemia, diabetes mellitus (DM), obesity and systemic inflammation are risk factors for atherosclerosis and increased vascular stiffness. Arterial stiffness, which occurs as a result of thickening of the arterial wall and loss of elasticity, has become an indicator of atherosclerosis (4). In hypertensive patients with renal failure and patients with coronary artery disease (CAD), arterial stiffness is a marker of morbidity (infarction, fatal stroke) and cardiovascular mortality. Cardiovascular toxicity is a cause of early morbidity and mortality after treatment with chemotherapeutic agents in cancer patients. Arterial stiffness can be used as a marker to predict subclinical cardiovascular damage (5).

The aim of our study is to investigate the factors affecting the level of arterial stiffness in cancer patients receiving immunotherapy in our clinic. There are no publications in the literature regarding the investigation of factors affecting arterial stiffness levels in patients who have previously received immunotherapy.

MATERIALS AND METHODS

This study was conducted prospectively by obtaining informed voluntary consent forms from 42 patients aged between 18-80 years who were diagnosed with malignant melanoma, lung cancer, RCC and received immunotherapy treatment and who applied to Adnan Menderes University Faculty of Medicine Medical Oncology Clinic between 01.06.2021 and 01.06.2022.

At the time of the first application, weight, height, age, BMI, sex, type of cancer, previous treatment received for cancer, agents used in the treatment received, current immunotherapy agents used, comorbid conditions, smoking history of the patients receiving immunotherapy were recorded and arterial stiffness levels were measured.

The effects of these factors on arterial stiffness were evaluated. BMI was calculated for the patients whose height and weight were measured using the weight (kg) / height² (m²) formula. The patients' smoking status was evaluated as "smoker-nonsmoker" and their comorbidity status was evaluated as "additional disease-no additional disease" and recorded. This disease was also recorded in those with additional diseases.

Following the first measurement, the patients were seen again in the third and sixth cycles, and their measurements were repeated and recorded. The measured data of the patients including pulse wave velocity (PWV), augmentation index (Alx), diastolic blood pressure (mmHg), systolic blood pressure (mmHg), mean arterial pressure (mmHg), heart rate (minute), pulse pressure (mmHg), stroke volume (ml), cardiac output (l/min), peripheral resistance (s*mmHg/ml), cardiac index (l/min*1/m²), reflection magnitude (%), augmentation pressure (mmHg), were recorded using the brachial cuff based oscillometric device Mobil-OGraph (IEM, Stolberg, Germany) and HMS CS (Hypertension Management System Client Server) software system.

Statistical analysis

The IBM-SPSS Statistics 23 program was used for statistical analysis. Descriptive statistics were presented as numbers and percentages for categorical variables and as mean, standard deviation, median, minimum and maximum for numerical variables. For numerical variables, ANOVA Test was used in multiple independent group comparisons when the normal distribution assumption was met; T Test was used in pairwise independent group comparisons when the normal distribution assumption was met. Pearson test was used for correlations where normal distribution was achieved in the association between numerical data. General Linear Model Test was used to reveal the effect of the independent variable on the dependent variable. The statistical significance was set at p value less than 0.05.

RESULTS

Demographics of the subjects are summarized in Table 1; age, height, weight, BMI values are summarized in Table

MEANDROS MEDICAL AND DENTAL JOURNAL
March 2025 (1):101-107

Meandros Medical and Dental Journal
doi: 10.69601/meandrosmdj.1594499

Table 1. Demographics of the subjects

		N (%)
Age	65 years old>	22 (52.3)
	65 years old≤	20 (47.7)
Sex	Male	35 (83.3)
	Female	7 (16.7)
Smoking	Smoker	30 (71.4)
	Non-smoker	12 (28.6)
BMI	<30	37 (88.1)
	≥30	5 (11.9)
Cancer type	RCC	6 (14.3)
	Malignant melanoma	9 (21.4)
	Lung cancer	27 (64.3)
Immunotherapeutic agent	Nivolumab	41 (97.6)
	Pembrolizumab	1 (2.4)
Additional disease	No	18 (42.9)
	Yes	24 (66.1)
CT (Cancer treatment)	Received	30 (71.4)
	Not received	12 (28.6)
Tyrosine kinase inhibitor	Received	8 (19.0)
	Not received	34 (81.0)

2. Comparative evaluation of patient data is shown in Table 3. For each given parameter, the 1st measurement value, 2nd measurement value, and 3rd measurement value of the patients were recorded and no significant difference was found between the measurements.

Table 2: Age, height, weight, BMI values of the subjects

	Mean	Median	SD	Minimum	Maximum
Age	63.79	66.00	9.37	35.00	80.00
Height (cm)	168.81	168.50	9.20	145.00	185.00
Weight (kg)	72.33	70.00	15.27	52.00	110.00
BMI (kg/m²)	25.43	24.95	5.44	16.40	45.20

Table 4 summarizes the changes in pulse pressure measurements according to sex, smoking status and cancer type. When the pulse pressure of women was examined, it was found to be higher than that of men in the first measurement (p= 0.009). When the pulse pressures of smokers and non-smokers were compared, it was seen that the pulse pressure of smokers was higher (p= 0.007). While no significant difference was found when PWV measurements were compared according to cancer type in the study, a significant difference was found when pulse pressures were examined according to cancer type (p= 0.026). At the first measurement, the pulse pressure of patients with lung cancer was higher than that of patients with malignant melanoma and RCC. No correlation was found between the patients' BMI and PWV measurements (Table 5). However, when looking at age, it was seen that there was an increase in PWV as age increased (1st Measurement r:0.900, 2nd Measurement r:0.909 3rd Measurement r:0,907; all measurements p<0.01). As seen in Table 6, PWH of those with and without additional diseases were compared. PWV was higher in patients with additional diseases. However, when PWV was examined among patients with HT, DM, or CAD, no significant difference was found in PWV between the diseases.

DISCUSSION

In our study, we investigated the factors affecting the level of arterial stiffness in cancer patients who received immunotherapy as oncological treatment in our clinic. There are no publications in the literature regarding the investigation of factors affecting arterial stiffness in patients who have previously received immunotherapy.

Table 3: Comparative evaluation of patient data

n:42	1st measurement (mean±SD)	2nd measurement (mean±SD)	3rd measurement (mean±SD)	p
Systole (mmHg)	119.10±19.55	114.98±15.95	115.95±17.71	0.568
Diastole (mmHg)	77.98±13.36	75.17±12.91	75.64±75.64	0.990
MAP (Mean arterial pressure) (mmHg)	91.83±23.03	93.81±12.78	94.14±14.08	0.994
Pulse pressure (mmHg)	41.12±12.25	39.10±10.13	40.31±10.90	0.323
Pulse (1/min.)	76.86±14.50	75.24±14.57	75.02±15.35	0.848
Stroke volume (ml)	63.31±14.57	63.85±14.12	64.14±13.35	0.298
Cardiac output (L/min)	4.70±0.63	4.68±0.82	4.67±0.77	0.135
Environmental resistance	1.24±0.20	1.23±0.20	1.23±0.19	0.308
Cardiac index	2.59±0.46	2.58±0.59	2.60±0.57	0.198
PWV	9.01±1.54	8.94±1.39	8.91±1.43	0.636
Augmentation pressure	8.37±5.88	7.83±4.79	11.52±9.52	0.073
Reflection magnitude	59.30±11.33	60.16±8.56	62.50±11.04	0.104
Alx	23.11±12.33	22.00±11.37	22.92±12.45	0.117

Table 4: Change in pulse pressure measurement according to sex, smoking status and cancer type

	1st measurement (mean±SD)	3rd measurement (mean±SD)	p
SEX			
Male (n:35)	40.94±13.16	40.40±11.01	0.009
Female (n:7)	42.00±6.60	39.86±11.15	
SMOKING			
Smoker (n:30)	42.27±13.81	41.03±11.40	0.007
Non-smoker (n:12)	38.25±6.67	38.50±9.77	
CANCER TYPE			
Malignant melanoma (n:9)	39.00±7.29	41.11±10.37	0.026
RCC (n:6)	40.00±9.35	38.67±8.80	
Lung cancer (n:27)	42.07±14.17	40.41±11.77	

Table 5: Correlation between age, BMI and PWV measurements

	1st PWV	2nd PWV	3rd PWV
AGE			
r	0.900	0.909	0.907
p	<0.01	<0.01	<0.01
BMI			
r	0.032	0.088	-0.013
p	0.839	0.978	0.935

Table 6: PWV measurement of those with and without additional diseases

	1st measurement (mean±SD)	2nd measurement (mean±SD)	3rd measurement (mean±SD)
ADDITIONAL DISEASE			
With additional disease (n:24)	9.50±1.26	9.45±1.13	9.38±1.15
Without additional disease (n:18)	8.36±1.67	8.26±1.43	8.27±1.56
p	0.016	0.004	0.011

breast cancer patients and control group patients, it was found that the mean pulse wave velocity was higher in breast cancer patients. Pulse wave velocity was significantly higher in patients taking aromatase inhibitors (5).

In the study conducted by Visvikis et al., in which 70 colorectal cancer patients receiving adjuvant FOLFOX/XELOX treatment were included, cardiovascular evaluation was performed at the beginning and end of chemotherapy. Carotid-radial PWV, carotid-femoral PWV and AIx were found to be significantly higher in patients after chemotherapy ($p<0.001$). These results were found to be significant when examined separately in each treatment subgroup. (6).

In our study, PWV was measured in patient with RCC, malignant melanoma and lung cancer patients receiving immunotherapy. No difference was found in terms of PWV among cancer types. No significant difference was found between the immunotherapy agent used and PWV. In the study conducted by Novo et al. to evaluate the subclinical vascular effects of anthracyclines and trastuzumab (TRZ), it was observed that in patients treated with anthracycline-containing chemotherapy, arterial stiffness indices increased significantly at 3 months, but not at 6 or 12 months, when anthracycline treatment was discontinued and patients were under treatment with taxanes and TRZ. There was no significant change in blood pressure values during follow-up. Changes in arterial stiffness parameters in patients occur immediately after initiation of anthracycline therapy and are thought to be reversible when anthracycline therapy is discontinued. (7).

In our study, the patients' parameters were measured and evaluated at the beginning of the immunotherapy treatment and in the 3rd and 6th cycles. No significant difference was found between immunotherapy agents and PWV measurements. The effects of immunotherapy agents (nivolumab, pembrolizumab) on arterial stiffness have not yet been demonstrated.

In a review by Smulyan et al., mean systolic blood pressure was found to be lower in women than in men. However, systolic blood pressure increased linearly and significantly with age in both men and women. Regarding diastolic blood pressure, lower values were found in women than in men, and there was a significant increase in this parameter with age. In the same study, when PWV was examined in diabetics and non-diabetics, it was significantly higher in diabetics than in non-diabetics (8).

In our study, there was no significant difference in both systolic blood pressure and diastolic blood pressure between men and women. No significant difference was found when PWV was examined between diabetic and non-diabetic patients.

In the study conducted by Demir et al. including 110 patients diagnosed with Type 2 DM without a history of coronary artery disease, PWV values were found to be higher in those receiving antihypertensive treatment. In the same study, no statistically significant difference was found between BMI and PWV (9). In the study conducted by Theilade et al., PWV was found to be statistically significantly higher in patients with a history of coronary artery disease than in patients without coronary artery disease ($p<0.001$) (10). In the study conducted by Dahlen et al . , a statistically significant positive correlation was found between PWV and BMI ($p=0.001$; $r=0.127$; $r=0.175$, respectively) (11). In the study by Evans et al. examining a cohort of patients meeting the criteria for stage 3 chronic kidney disease, a statistically significant negative association was found between BMI and PWV ($p<0.001$) (12).

In our study, PWV was higher in patients with additional diseases such as HT, DM and CAD than in those without. However, when PWV was examined among patients with any of HT, DM, or CAD, no significant difference was found between the diseases. In our study, similar to the study by Demir et al., no statistically significant difference was found between BMI and PWV.

A review by Dupont et al also found that women had greater increases in pulse pressure and wave reflection compared with men of the same age (13). In our study, when we looked at pulse pressure, pulse pressure was higher in women than in men. When PWV was examined, no significant difference was found in PWV when men and women were compared. However, an increase in PWV was also detected as age increased.
In a comparative study by Rehill et al. of AIx and PWV measured in smokers and the period after these patients quit smoking, AIx was significantly higher in smokers.

However, there was no significant difference in PWV (14). In our study, there was no significant difference in PWV measurement between smokers/nonsmokers; there was no significant difference in AIx measured in smokers/nonsmokers. In our study, pulse pressure was higher in smokers than in nonsmokers.

CONCLUSION

In conclusion, our study, it was found that smoking, sex and cancer type had an effect on pulse pressure changes in cancer patients receiving immunotherapy, that there was no significant difference in other factors; PWV increased with age; and PWV was higher in those with additional diseases.

The limitations of our study include the small number of patients and the fact that immunotherapy agents could not be compared with the same number of patients. There are no previous publications in the literature regarding the investigation of factors affecting arterial stiffness levels related to immunotherapy. The use of promising immunotherapy agents in oncological treatments is increasing and more studies are needed to determine factors affecting the level of arterial stiffness.

Acknowledgments
Adnan Menderes University Faculty of Medicine Medical Oncology Clinic staff

Authorship contributions
EEGY, MBA and EO designed the study; EEGY and MBA collected the data and carried out statistical analysis; EEGY, MBA performed the literature search; BD, MT and EO supervised the study; MBA, EEGY, and EO prepared and revised the manuscript. All authors gave the final approval of the version to be published.

Data availibility statement
The data that support the findings of this study are available from the corresponding author, [E.O.], upon reasonable request.

Declaration of competing interest
The authors have no conflicts of interest to declare.

Ethics
Ethics committee approval was obtained from the Clinical Research Ethics Committee of Adnan Menderes University Faculty of Medicine (Protocol No: 2021/74 Approval Date: 14.06.2021).

Funding
This study is from Emine Esra Güner Yıldırım 's internal medicine specialization thesis, and the thesis was supported by Adnan Menderes University Scientific Research Projects (BAP) Unit with project number TPF-21035.

REFERENCES

1. Mellman I, Coukos G, Dranoff G. Cancer immunotherapy comes of age. Nature. 2011;480(7378):480-9.
2. Matts C, Beck A. Immunotherapy-Related Adverse Effects When Treating Cancer# 375. Journal of Palliative Medicine. 2019;22(6):724-5.
3. Cecelja M, Chowienczyk P. Role of arterial stiffness in cardiovascular disease. JRSM cardiovascular disease. 2012;1(4):1-10.
4. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. J Am Coll Cardiol. 2010;55(13):1318-27.
5. Yersal Ö, Eryilmaz U, Akdam H, Meydan N, Barutca S. Arterial stiffness in breast cancer patients treated with anthracycline and trastuzumab-based regimens. Cardiology Research and Practice. 2018;2018.
6. Visvikis A, Kyvelou S, Pietri P, Georgakopoulos C, Manousou K, Tousoulis D, et al. Cardiotoxic profile and arterial stiffness of adjuvant chemotherapy for colorectal cancer. Cancer Management and Research. 2020;12:1175.
7. Novo G, Di Lisi D, Manganaro R, Manno G, Lazzara S, Immordino FA, et al. Arterial stiffness: effects of anticancer drugs

MEANDROS MEDICAL AND DENTAL JOURNAL
March 2025 (1):101-107

Meandros Medical and Dental Journal
doi: 10.69601/meandrosmdj.1594499

used for breast cancer women. Frontiers in Physiology. 2021;12:661464.

8. Smulyan H, Lieber A, Safar ME. Hypertension, diabetes type II, and their association: role of arterial stiffness. American journal of hypertension. 2016;29(1):5-13.

9.Demir B, Sezer SD, Topaloğlu Ö, TAŞKIRAN E, Burcu I, SOYALTIN U, et al. The relationship between nephropathy, retinopathy, obesity and arterial stiffness in type 2 diabetes mellitus. İstanbul Bilim Üniversitesi Florence Nightingale Tıp Dergisi. 2015;1(2):59-67.

10. Theilade S, Lajer M, Persson F, Joergensen C, Rossing P. Arterial stiffness is associated with cardiovascular, renal, retinal, and autonomic disease in type 1 diabetes. Diabetes care. 2013;36(3):715-21.

11. Dahlén EM, Tengblad A, Länne T, Clinchy B, Ernerudh J, Nystrom F, et al. Abdominal obesity and low-grade systemic inflammation as markers of subclinical organ damage in type 2 diabetes. Diabetes & metabolism. 2014;40(1):76-81.

12. Evans PD, McIntyre NJ, Fluck RJ, McIntyre CW, Taal MW. Anthropomorphic measurements that include central fat distribution are more closely related with key risk factors than BMI in CKD stage 3. PLoS One. 2012;7(4):e34699.

13. DuPont JJ, Kenney RM, Patel AR, Jaffe IZ. Sex differences in mechanisms of arterial stiffness. British journal of pharmacology. 2019;176(21):4208-25.

14. Rehill N, Beck CR, Yeo KR, Yeo WW. The effect of chronic tobacco smoking on arterial stiffness. British journal of clinical pharmacology. 2006;61(6):767-73.