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Research Article

Burnout syndrome and associated factors among healthcare workers in COVID-19 contact tracing teams: A cross-sectional study from Türkiye

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Abstract

Objective: The aim of this study is to investigate levels of occupational burnout, anxiety, and quality of life among healthcare workers engaged in contact tracing activities during the pandemic.

Method: This cross-sectional study was conducted in a provincial center in southern Türkiye. Between September 2021 and April 2022, 210 healthcare professionals actively serving in contact tracing teams were recruited into the study. Participants were given a questionnaire covering sociodemographic information, the Maslach Burnout Inventory, and the Health Workers' Work-Life Quality Scale. Inferential analyses included the chi-square test, Student's t-test, Mann–Whitney U test, one-way ANOVA, the Kruskal–Wallis test and linear regression analysis.

Results: The mean age of the 210 participants was 39.8 years and 73.8% were female and 26.2% were male. Physicians reported lower quality-of-life scores than others. Men exhibited higher scores on the depersonalization subscale than women. Physicians and dentists scored higher on the depersonalization subscale than other occupational groups. Professionals who lived outside their homes during the contact tracing period had higher anxiety, emotional exhaustion, and depersonalization scores, as well as lower personal accomplishment scores, than those who lived at home. Healthcare professionals assigned to swab collection duties reported higher emotional exhaustion and depersonalization scores than those not performing such tasks.

Conclusions: Of all the professional groups studied, physicians exhibited the highest burnout levels and the lowest quality-of-life scores. Additionally, healthcare professionals assigned to swab collection duties demonstrated significantly higher burnout levels. These results highlight the urgent need for targeted psychosocial support, workload management, and protective interventions.

Keywords: COVID-19, Pandemics, Health Personnel, Burnout, Anxiety, Quality of Life.

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INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the seventh known human coronavirus. It was first identified in January 2020 during a pneumonia outbreak in Wuhan, China. On March 10, 2020, the Turkish Ministry of Health announced to the public that the virus had arrived in Türkiye (1). On March 11, 2020, the World Health Organization (WHO) officially declared a pandemic (2). As of April 2022, approximately 492 million cases and 6.1 million deaths had been recorded globally. In Türkiye, the respective figures were approximately 14.9 million and 98 thousand (3).

Contact tracing is a process conducted in the field that involves systematically tracking the source of an infection and the contacts of reported cases during an epidemic. Super-spreader cases in the ongoing pandemic have once again highlighted the critical role of contact tracing in controlling the disease. Contact tracing teams are responsible for evaluating possible and confirmed cases, taking samples, and implementing necessary treatment and isolation measures in the patients' homes (4,5).

During the pandemic, healthcare workers on the front lines faced severe psychological pressure in addition to deteriorating working conditions. Similarly, high rates of anxiety, depression, and sleep disorders were observed among frontline healthcare personnel during previous SARS and MERS outbreaks. Moreover, these effects persisted long after the outbreaks ended (6, 7). According to data collected in China during the pandemic, 50% of healthcare professionals interviewed reported symptoms of depression. Furthermore, healthcare workers, including doctors, exhibit higher rates of insomnia, anxiety, depression, somatization disorder, and obsessive-compulsive symptoms (8). A study by Lai et al. found that many participants exhibited symptoms of depression, anxiety, insomnia, and distress. Another study conducted in China during the pandemic found a 25.2% prevalence rate among 14,825 doctors and nurses in 31 Chinese provinces (9).

Burnout syndrome is a work-related problem characterized by emotional, physical, and mental exhaustion resulting from prolonged exposure to intense stress, as well as a substantial decline in self-esteem and perceived competence (10). First conceptualized by Freudenberger in 1974, burnout syndrome affects approximately 10% of the workforce in European Union countries and 17% outside of them. The rate has significantly increased among healthcare workers during the pandemic (11). Furthermore, 521 healthcare workers lost their lives in Türkiye during the pandemic.

This study examined burnout, anxiety, and quality of life levels among healthcare workers on contact tracing teams during the pandemic, as well as the sociodemographic, occupational, and individual factors that influence these levels.

METHODS

Research Area

The research was conducted in Adana, the seventh most populous province in Türkiye. According to 2021 Turkish Statistical Institute (TUIK) data, the province has a population of approximately 2,263,373 and comprises 15 districts, five of which are central. The study focused on four of these central districts: Seyhan, Yüreğir, Çukurova, and Sarıçam. Contact tracing teams operated within the district health directorates of these districts. The team structure consisted of three levels: management, central, and field.

Research Type and Ethical Permissions

This is a single-center, cross-sectional study. Ethical approval was obtained from the Çukurova University Faculty of Medicine Ethics Committee on February 12, 2021 (meeting no. 108, decision no. 39). Additionally, permissions were obtained from the Scientific Research Platform of the Republic of Türkiye's Ministry of Health (February 6, 2021) and the Adana Provincial Health Directorate (March 18, 2021). Throughout the research, compliance with the latest versions of the Good Clinical Practice

Guidelines and the Helsinki Declaration was ensured, and informed consent was obtained from all participants.

Population and Sample

The research population was defined as 640 people. Using a 95% confidence level, 80% power, and an effect size of d = 0.389, the target sample size was calculated to be 210 participants. Due to the dynamic nature of the teams and constant changes to the employee list, a non-probability sampling method was employed.

Measuring Instruments

The study used three scales and a personal information form.

The Coronavirus Anxiety Scale (CAS): This five-item scale, developed by Lee, is based on thoughts from the past two weeks. The scoring range is 0–20, with higher scores indicating higher anxiety levels. Cronbach's alpha = 0.832 (12). The Turkish validity and reliability study of the scale was conducted by Akkuzu et al (13).

Maslach Burnout Scale (MBS): This scale was developed by Maslach et al. The MBS is a scale that evaluates three sub-dimensions based on 22 items: Emotional Exhaustion (EE)—9 items; Depersonalization (DP)—5 items; and Personal Accomplishment (PA)—8 items. A Likert-type scale was used, with 0 indicating "Never" and 4 indicating "Always"; the PA subscale was reverse-scored. High scores on the EE and D subscales and low scores on the PA subscale indicate the intensity of burnout. Cronbach's alpha = 0.93 (14). The Turkish adaptation of the scale and the validity-reliability study were carried out by Ergin (15).

Health Personnel Working Life Quality Scale (HPLQS): Developed by Aydın et al. (16) (2011) in Turkish, the HPLQS consists of 27 questions and six factors: (F1) workplace accidents and physical working conditions; (F2) workplace discrimination; (F3) opportunities for continuous development; (F4) social integration into the organization; (F5) work stress and time pressure; and (F6) laws within the organization. The scale uses a 1–5 Likert scale; raw scores are standardized using the formula (raw score/maximum score) × 100 (range: 20–100). As the total score increases, so does the quality of life. Factor loadings ranged from 0.58 to 0.83, and Cronbach's alpha was 0.882.

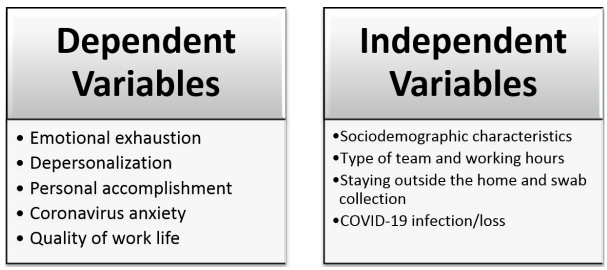

Figure 1. Dependent and Independent Variables

Data Collection

The surveys were conducted in person during the hours when the contact tracing teams were together, either at the start of their morning shift or when they returned to the institution at the end of the day. Due to the dynamic structure of the teams and the high volume of temporarily assigned personnel, the surveys included both active and former contact tracing healthcare workers. Figure 1 shows the dependent and independent variables of the study.

Data Analysis

All analyses were performed using the SPSS 22 software package. Descriptive statistics are presented as n and percentage for categorical variables and as mean ± standard deviation or median (interquartile range [IQR]) for continuous variables. Normality was assessed using the Kolmogorov-Smirnov test. The Student t-test was applied to data conforming to a normal distribution for pairwise group comparisons, and the Mann-Whitney U test was applied to data that did not conform to a normal distribution. For multiple group comparisons, one-way ANOVA was applied to normally distributed data, and the Kruskal–Wallis test was applied to non-normally distributed data. The Pearson and Spearman methods were used for the respective pairwise correlation analyses; linear regression analysis was applied to determine predictors of the dependent variable. The statistical significance level was set at $p < 0.05$.

RESULTS

The participants' average age was 39.8 ± 9.1 years (range: 23–60 years), and 71% of them had children. Among the healthcare workers, 36 (17.1%) were physicians, 22 (10.5%) were dentists, and 132 (62.9%) were non-physician healthcare personnel. Sixteen healthcare workers (7.6%) had to stay outside their own homes during contact tracing. Of the participants, 125 (59.5%) collected swab samples from patients during their assignment. Furthermore, 47.6% were not actively working in the field but rather from the center.

Table 1. Comparing quality of life scores based on participants' characteristics and work styles.

Participants' characteristics and work styles		Quality of life	
		x̄±SS	p*
Gender	Female	84.6±11.9	0.163
	Male	82.1±11.0	
Marital status	Single	79.9±12.6	0.097
	Married	84.3±11.3	
	Others	87.6±13.6	
Having children	Yes	84.6±11.7	0.212
	No	82.4±11.7	
Profession	Medical doctor	78.6±9.7	**0.002**
	Dentist	87.7±10.8	
	Non-physician healthcare personnel	85.4±11.8	
	Others	79.7±11.7	
Living together	Alone	79.9±17.7	0.160
	With family	84.3±11.1	
The sector in which the husband/ wife works	Single	79.9±12.6	**0.016**
	Health	83.9±11.9	
	Non-health	86.1±10.5	
	Unemployed	78.4±13.2	
Staying outside your own home	Yes	87.6±8.6	0.200
	No	83.7±11.9	
Swab collection situation	Yes	83.8±11.9	0.850
	No	84.1±11.4	
Satisfaction with working hours	I'm not satisfied at all	85.3±13.7	**0.002**
	I'm not satisfied	87.1±8.8	
	I'm undecided	78.8±14.2	
	I'm satisfied	84.6±9.6	
	I'm very satisfied	90.0±8.0	
Work routine	Permanent daytime work	83.1±10.8	0.094
	Night shift	82.3±12.2	
	Shift work	85.8±12.8	
	Mixed	91.9±8.6	

* Student T-test was used if there were two categories, and One Way ANOVA test was used if there were more than two categories.

A significant difference in total quality of life scores was found among occupational groups ($p = 0.002$, $\eta^2 = 0.7$). Physicians' scores were significantly lower than those of dentists and auxiliary health personnel (Table 1). Women had significantly higher F3 (opportunities for continuous development) scores than men ($p = 0.029$, $r = 0.31$), as did those with children ($p = 0.008$). Individuals living with

their families had significantly higher F3 (opportunities for continuous development) scores than those living alone ($p = 0.014$, $r = 0.25$). Those stay outside their homes during contact tracing scored higher on F1 (physical working conditions) and F5 (work stress) ($p = 0.045$, $r = 0.31$; $p = 0.029$, $r = 0.32$). Healthcare workers who collected swabs had significantly higher physical working conditions scores. Conversely, F3 (opportunities for continuous development) ($p = 0.009$, $r = 0.40$), F4 (social integration into the organization) ($p = 0.0.16$, $r = 0.29$), and F6 (laws in the organization) ($p = 0.004$, $r = 0.41$) scores were significantly lower. Satisfaction with working hours emerged as a factor that determined overall quality of life and all its sub-factors (F1 $p = 0.028$, $\eta^2 = 0.6$; F2 $p < 0.001$, $\eta^2 = 0.11$; F3 $p < 0.001$, $\eta^2 = 0.10$; F4 $p = 0.002$, $\eta^2 = 0.6$; F5 $p < 0.001$, $\eta^2 = 0.12$).

Men had significantly higher depersonalization scores than women ($p = 0.015$, $r = 0.28$). Participants with children had lower depersonalization scores ($p = 0.003$, $r = 0.36$) and higher personal accomplishment scores ($p < 0.001$, $r = 0.52$). Significant differences in emotional burnout scores were found between high school graduates and those with a master's or doctoral degree ($p = 0.014$, $\eta^2 = 0.8$). The most striking finding among occupational groups was that physicians and dentists had significantly higher depersonalization scores than auxiliary healthcare personnel ($p < 0.001$, $\eta^2 = 0.9$). Conversely, auxiliary healthcare personnel had higher personal accomplishment scores than physicians ($p < 0.001$, $\eta^2 = 0.9$). The group with perceived low monthly income had significantly higher emotional exhaustion and depersonalization scores than the middle and high income groups ($p = 0.004$, $\eta^2 = 0.5$; $p = 0.024$, $\eta^2 = 0.6$) (Table 2).

Those who remained outside their homes during the contact tracing process had significantly higher emotional exhaustion ($p = 0.01$, $d = 0.71$) and depersonalization ($p < 0.001$, $r = 0.74$) scores and significantly lower personal accomplishment scores ($p = 0.015$, $r = 0.51$). Additionally, emotional exhaustion ($p = 0.015$, $d = 0.35$) and depersonalization ($p = 0.043$, $r = 0.29$) were found to be significantly higher in healthcare workers who collected swabs. A significant increase in burnout subscale scores was observed as satisfaction with working hours decreased (emotional exhaustion $p < 0.001$, $\eta^2 = 0.14$; depersonalization $p < 0.001$, $\eta^2 = 0.12$; personal accomplishment $p = 0.002$, $\eta^2 = 0.08$) (Table 2).

No significant relationship was found between sociodemographic variables and Coronavirus Anxiety Scores. However, individuals outside their homes during contact tracing had significantly higher anxiety scores than those who were not ($p < 0.001$, $d = 0.37$). Additionally, anxiety scores were significantly higher among those who were dissatisfied with their working hours compared to those who were satisfied ($p = 0.028$, $\eta^2 = 0.08$).

A significant positive correlation was found between quality of life, years worked, and personal accomplishment. A significant positive correlation was found between anxiety level and emotional exhaustion and depersonalization. A significant negative correlation was found between personal accomplishment and depersonalization and emotional exhaustion (Table 3).

A multiple linear regression analysis was conducted to estimate the relationship between the subdimensions of the Maslach Burnout Inventory (MBI) and the Quality of Working Life Inventory. Scores on F2 (workplace discrimination), F3 (development and improvement opportunities), and F5 (work stress and time pressure) were found to predict emotional exhaustion. Additionally, scores on F3 and F5 were found to predict depersonalization, and scores on F3 and F6 (organizational laws) were found to predict personal accomplishment (Table 4).

DISCUSSION

The effects of the pandemic were felt in all aspects of life, causing changes in working conditions for various professional groups, whether directly or indirectly. Healthcare workers were among those most affected by the pandemic. Burnout is more prevalent in professions that require intensive human interaction (17). Healthcare workers, who constantly interact with people in the service sector, are among the groups most exposed to burnout (18). Dealing with human life and the sense of responsibility that comes with it causes healthcare workers to experience intense work-related stress (19).

Table 2. Comparison of burnout scores according to demographic characteristics.

Demographic characteristics		Emotional exhaustion		Depersonalization		Personal accomplishment	
$\bar{x}$±SS		p*	Median (IQR)	p**	Median (IQR)	p**	
Gender	Female	19.7±7.6	0.200	5.0 (2.0-7.0)	**0.015**	21.0 (17.0-26.0)	0.849
	Male	17.9±9.3		7.0 (3.0-11.0)		22.0 (18.0-25.0)	
Having children	Yes	18.8±8.1	0.232	4.0 (2.0-7.5)	**0.003**	23.0 (19.0-26.0)	**<0.001**
	No	20.2±8.1		7.0 (4.0-10.0)		19.0 (15.0-22.0)	
Educational status	High school and below	14.4±10.6	**0.014**	4.5 (1.0-11.0)	0.235	23.0 (13.0-27.0)	0.629
	Associate degree / Bachelor's degree	19.1±8.2		5.0 (2.0-8.0)		22.0 (18.0-26.0)	
	Master's degree / Doctorate	20.9±6.3		6.0 (4.0-10.0)		20.0 (16.0-25.0)	
Profession	Medical doctor	21.5±7.2	0.132	9.0 (6.0-11.0)	**<0.001**	17.5 (14.5-24.0)	**0.002**
	Dentist	20.9±8.6		7.0 (4.0-10.0)		20.0 (17.0-24.0)	
	Non-physician healthcare personnel	18.5±8.2		4.0 (1.0-7.0)		23.0 (18.0-27.0)	
	Others	17.7±8.2		6.0 (3.0-10.5)		21.5 (18.5-24.0)	
Monthly income status	Bad	21.5±7.4	**0.004**	6.0 (4.0-10.0)	**0.024**	21.0 (17.0-25.0)	0.697
	Average	18.1±8.2		4.0 (1.0-8.0)		23.0 (17.0-26.0)	
	Good	16.3±8.4		4.0 (1.0-8.0)		20.0 (16.0-28.0)	
Living together	Alone	20.3±7.7	0.592	5.0 (1.0-9.0)	0.725	18.0 (15.0-20.0)	**0.017**
	With family	19.1±8.2		5.0 (3.0-9.0)		22.0 (18.0-26.0)	
Staying outside your own home	Yes	24.2±6.9	**0.01**	11.5 (9.5-14.0)	**<0.001**	18.0 (14.5-21.0)	**0.015**
	No	18.8±8.1		5.0 (2.0-8.0)		22.0 (18.0-26.0)	
Swab collection situation	Yes	20.3±8.0	**0.015**	6.0 (3.0-10.0)	**0.043**	21.0 (16.0-26.0)	0.089
	No	17.5±8.0		4.0 (2.0-7.0)		22.0 (19.0-26.0)	
Work routine	Permanent daytime work	18.8±8.1	0.647	5.0 (1.0-9.0)	0.393	21.0 (18.0-25.5)	0.438
	Night shift	18.7±8.8		6.0 (4.0-10.0)		23.0 (18.0-28.0)	
	Shift work	20.0±7.4		5.0 (3.0-7.5)		20.0 (16.0-25.0)	
	Mixed	21.8±9.2		5.0 (3.0-5.5)		21.0 (17.5-25.5)	
Satisfaction with working hours	I'm not satisfied at all	24.9±8.7	**<0.001**	7.5 (4.0-12.0)	**<0.001**	21.0 (16.0-26.0)	**0.002**
	I'm not satisfied	21.5±6.3		6.0 (4.0-10.0)		21.0 (18.0-25.0)	
	I'm undecided	18.8±7.5		6.0 (3.0-9.0)		18.5 (15.0-24.0)	
	I'm satisfied	15.8±7.9		3.0 (1.0-6.0)		24.0 (20.0-27.0)	
	I'm very satisfied	16.5±10.1		7.0 (1.0-14.0)		20.0 (16.0-27.0)	

* Student T-test was used if there were two categories, and One Way ANOVA test was used if there were more than two categories;
** The Mann-Whitney U Test was used if there were two categories, and the Kruskal-Wallis Test was used if there were more than two categories.

Table 3. Correlation results between age, years of work experience, and scale scores.

		Age	Years of work experience	Quality of life	Anxiety Level	Emotional exhaustion	Depersonalization
Years of work experience	r	**0.883**					
	p	**<0.001**					
Quality of life	r	0.080	**0.143**				
	p	0.256	**0.040**				
Anxiety Level	r	0.030	0.028	**0.161**			
	p	0.664	0.691	**0.021**			
Emotional exhaustion	r	**-0.178**	-0.117	0.091	**0.266**		
	p	**0.010**	0.092	0.196	**<0.001**		
Depersonalization	r	**-0.304**	**-0.338**	-0.064	**0.232**	**0.568**	
	p	**<0.001**	**<0.001**	0.360	**0.001**	**<0.001**	
Personal accomplishment	r	**0.365**	**0.360**	**0.244**	-0.061	**-0.223**	**-0.437**
	p	**<0.001**	**<0.001**	**<0.001**	0.381	**0.001**	**<0.001**

Table 4. Work Life Quality Parameters That Can Predict Burnout Levels.

Emotional exhaustion R^2=0.276				**Depersonalization** R^2=0.178			**Personal accomplishment** R^2=0.242		
	Unstandardized Coefficients		Sig.	Unstandardized Coefficients		Sig.	Unstandardized Coefficients		Sig.
	B	Std. Error		B	Std. Error		B	Std. Error	
F1	0.034	0.093	0.714	0.015	0.057	0.790	0.084	0.066	0.206
F2	0.296	0.108	**0.007**	0.008	0.067	0.909	-0.064	0.077	0.408
F3	-0.500	0.149	**0.001**	-0.466	0.092	**<0.001**	0.676	0.106	**<0.001**
F4	-0.078	0.166	0.636	0.088	0.102	0.389	0.105	0.118	0.374
F5	0.825	0.226	**<0.001**	0.360	0.140	**0.011**	0.297	0.162	0.067
F6	0.116	0.216	0.591	0.074	0.134	0.582	-0.361	0.155	**0.021**

(F1) workplace accidents and physical working conditions; (F2) workplace discrimination; (F3) opportunities for continuous development; (F4) social integration into the organization; (F5) work stress and time pressure; and (F6) laws within the organization.

Pre-pandemic studies have also demonstrated high levels of burnout among healthcare workers (20,21). During the pandemic, their responsibilities and stress levels increased significantly. A study conducted in Hong Kong found that healthcare workers were at risk of burnout (22). Kökçü et al. found that healthcare workers experienced moderate levels of burnout in emotional exhaustion and personal accomplishment and low levels in depersonalization (23). Tukur et al. found that 86% of intensive care nurses working in tertiary care experienced emotional exhaustion, and approximately half of them experienced depersonalization (24).

Before the pandemic, a study was conducted on healthcare workers and found that their emotional exhaustion score was 17.8±8.12, their personal accomplishment score was 20.2±4.93, and their depersonalization score was 6.4±3.80 (25). Among primary care healthcare workers, the emotional exhaustion score was 14.63 ± 6.38, the personal accomplishment score was 10.80 ± 4.62, and the depersonalization score was 4.02 ± 3.15 (26). Sayıl et al. (27) found the emotional exhaustion score of healthcare workers at Ankara University Hospital to be 18.1, the personal achievement score to be 20.3, and the depersonalization score to be 5.48. Comparing the results of these studies with those of

our study suggests that the level of burnout among healthcare workers has increased since the pre-COVID-19 pandemic period.

The literature reports different results regarding burnout between genders. Some studies have found significant gender differences in emotional burnout (26), while others have not (28,29). A study conducted at the Diyarbakır Gazi Yaşargil Training and Research Hospital found that emotional burnout and personal accomplishment scores were significantly higher in women than in men (11). Mete et al., in a cross-sectional study conducted among physicians in primary and secondary healthcare settings in Türkiye, reported that emotional exhaustion was significantly more prevalent among female physicians, while depersonalization did not differ significantly by gender (30). In our study, men's depersonalization subscale scores were significantly higher than women's, but no significant differences were found in emotional burnout or personal accomplishment scores.

Consistent with previous studies, no significant differences were found in emotional exhaustion, depersonalization, or personal accomplishment based on marital status (11,25,26). In our study, significant differences in depersonalization and personal accomplishment were found based on having children, but no significant difference was found in emotional exhaustion. Healthcare workers with children reported feeling more sensitive and successful in their work. In a study by Tunç et al., physicians had higher emotional exhaustion scores, while nurses and midwives had higher personal accomplishment scores (11). Some studies have found that physicians' emotional exhaustion and depersonalization scores are significantly higher than those of other professional groups (11,25). In our study, physicians' depersonalization scores were significantly higher, while personal accomplishment scores were significantly higher in auxiliary healthcare personnel.

This study found that the emotional exhaustion and depersonalization scores of individuals with low incomes were significantly higher than those of other groups. In addition to an increased workload and stress during the pandemic, economic problems also contributed to healthcare workers experiencing burnout. Personal accomplishment scores were found to be significantly higher among those living with their families. Another study found that emotional exhaustion and depersonalization scores were significantly higher for those living alone than for those living with their families (31).

The study found that individuals outside their homes during contact tracing had significantly higher emotional exhaustion and depersonalization scores and significantly lower personal accomplishment scores. Similarly, those who collected swabs had higher scores for emotional exhaustion and depersonalization. Healthcare workers in this role may be more susceptible to burnout due to the technical challenges of collecting swabs and the necessity of close patient contact. In Gün's study, emotional exhaustion and depersonalization scores decreased and personal accomplishment scores increased as the average age increased (31). However, some studies have not found significant differences between age groups (32,33).

Studies have shown that as length of service in a profession increases, depersonalization scores decrease significantly (31-33). Similarly, our study found a significant positive correlation between years of service and personal accomplishment scores and a significant negative correlation between depersonalization scores and personal accomplishment scores. Previous studies have reported that being young and having little professional experience increases the risk of burnout (34,35). In our study, a significant positive correlation was found between anxiety and emotional exhaustion and depersonalization scores. Thus, it can be said that burnout increases as anxiety increases. A significant positive correlation was found between emotional exhaustion and depersonalization and a significant negative correlation was found between emotional exhaustion and personal accomplishment. Thus, it was determined that burnout negatively affects personal accomplishment.

According to profession, the "risk of work accidents, occupational diseases, and physical working conditions in the workplace" score was significantly higher among dentists. The "opportunities for continuous development and improvement" score was significantly higher among auxiliary health personnel. Those who stayed outside their homes during the contact tracing process had significantly higher scores for "Risk of Work Accidents, Occupational Diseases, and Physical Working Conditions in the Workplace" and "Work Stress and Time Pressure." Those who worked continuously during the day had significantly lower "Risk of Work Accidents, Occupational Diseases and Physical Working Conditions in the Workplace" scores compared to those who worked shifts. In Saygılı et al.'s study, those who worked on-call duties had significantly lower scores compared to those who did not (36). Supporting our findings, Mete et al. demonstrated that work stress and time pressure was the single strongest predictor of burnout among physicians, accounting for 35.4% of the variance in burnout scores. Occupational accident and physical working conditions risk contributed an additional 4%. These results, obtained using the same quality of work life scale employed in the present study, corroborate the central role of work stress and the quality of the working environment in the development of burnout among healthcare professionals (30).

Limitations of the Study

Healthcare workers involved in contact tracing teams were professionally exposed to the virus and could not be included in the study when they were absent from duty due to infection. Because the team structure, number of employees, and field areas were constantly changing, it was impossible to create a fixed employee list. This necessitated the adoption of a non-probability sampling method. The practice of temporary assignments constantly transformed the population structure, making it difficult to accurately calculate the population size.

Strengths of the Study

Collecting data face-to-face in the field significantly increased the reliability of the information. The research was conducted with the approval of the ethics committee, the Ministry of Health, and the Provincial Health Directorate. Using scales with proven validity and reliability added a high level of credibility to the findings.

CONCLUSION

This study demonstrated that burnout syndrome was a significant problem among healthcare workers involved in contact tracing during the pandemic, with physicians experiencing the highest burnout levels and lowest quality of life scores. Healthcare workers who stayed away from home and those performing swab collection were particularly vulnerable to emotional exhaustion and depersonalization. Workplace discrimination, limited development opportunities, and job stress emerged as key predictors of burnout dimensions. These findings highlight the urgent need for targeted psychosocial support programs, workload management strategies, and policy-level interventions — particularly for high-risk groups such as physicians and swab collection personnel. Future research should examine the long-term effects of burnout and evaluate the effectiveness of such interventions across different pandemic periods and healthcare settings.

Based on the findings of this study, several recommendations can be made at both institutional and national levels. At the institutional level, psychosocial support programs — including regular psychological counseling and peer support groups — should be established specifically for healthcare workers assigned to high-risk roles such as contact tracing and swab collection. Workload distribution should be reorganized to prevent excessive burden on physicians, and rotation systems should be implemented to minimize prolonged separation from home. At the national level, the Turkish Ministry of Health should develop standardized burnout monitoring protocols to be integrated into

public health emergency response plans. Given Türkiye's geographically and demographically diverse healthcare infrastructure, regional health directorates should tailor these interventions according to local workforce capacity and needs. Finally, collaboration between universities, public health institutions, and policymakers is encouraged to design and evaluate evidence-based intervention programs that can be rapidly deployed during future public health emergencies.

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Conflict of Interest

The authors declare that they have no conflict of interests regarding content of this article..

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Ethical Declaration

Ethical approval was obtained from the Çukurova University Faculty of Medicine Ethics Committee on February 12, 2021 (meeting no. 108, decision no. 39). Additionally, permissions were obtained from the Scientific Research Platform of the Republic of Turkey's Ministry of Health (February 6, 2021) and the Adana Provincial Health Directorate (March 18, 2021).

Authorship Contributions

Concept: AÇ,EN , Design: AÇ,EN,HD, Supervising: AÇ,EN,DY, Financing and equipment: AÇ,EN, Data collection and entry: AÇ, Analysis and interpretation: AÇ,EN,DY,HD, Literature search: AÇ,EN,DY, Writing: AÇ,EN,DY, Critical review: AÇ,EN,DY, HD.

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Scientific Reports in Medicine

Research Article

Increased levels of high-sensitive Troponin-T after first dose of Adriamycin containing therapy may predict brain-type natriuretic rise after 6 months in patients with breast carcinoma

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Abstract

Objective: In this study, we aimed to investigate the usefulness of highly sensitive troponin-T (hs-TnT) levels for the early prediction of anthracycline-related cardiac stress and subclinical cardiac dysfunction.

Method: Patients newly diagnosed with breast cancer with normal cardiac function were randomized to our study. All patients had taken 240 mg/m2 adriamycin in 12 weeks. Brain-type natriuretic peptide (BNP) and hs-TnT levels were measured; echocardiography and tissue Doppler imaging was performed to all patients for 4 times: at baseline, 4-12 hours after first adriamycin dose, at 3 months and at 6 months.

Results: A total of 43 women (52.7±12.1 years) with breast cancer were included in our study. Brain natriuretic peptide elevation was observed in 8 patients, in which 2 of them showed symptoms and signs of overt heart failure. In the logistic regression analysis, hs-TnT levels (OR: 1.154; (0.974–1.336 in 95% CI) and BNP levels (OR: 1.009 (1.001-1.018 in 95 % CI) measured 12–24 hours after first adriamycin dose were independently associated with BNP rise at 6th month. Receiver operating curve analysis revealed a cut-off value of 12.85 ng/L for hs-TnT levels to predict BNP elevation at 6th month with 62.5% sensitivity and 85.7% specificity.

Conclusion: hs-TnT levels after first dose of adriamycin containing therapy higher than 18.65 ng/L was associated with BNP elevation at 6th month with a specificity of 97.1% in our patient group. Early hs-TnT elevation may represent a potential marker of chemotherapy-related cardiac dysfunction.

Keywords: Anthracycline, cardiotoxicity, highly sensitive troponin T, Breast Cancer

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INTRODUCTION

Breast cancer (BC) is the most frequently observed neoplasm in women. It also accounts for 15 % of all cancer deaths and is the second cause of death due to malignant diseases after lung cancer (1). Surgical excision, cytotoxic chemotherapy (CC), hormone blockade therapy, radiotherapy and molecular therapy are effective options in the treatment of BC. Cytotoxic chemotherapy as adjuvant therapy and for metastatic disease is the most important component of BC treatment and improves survival (2).

Anthracyclines are frequently used in adjuvant setting and also in metastatic disease. In case of her2/neu expression, trastuzumab is added to therapy and has been shown to decrease relapse rate (3,4). However, cardiovascular (CV) toxicity is seen with these drugs, with increased risk of mortality and morbidity. However, toxicity profiles of these two drugs are different: anthracyclines cause permanent myocardial damage, while trastuzumab causes transient/reversible cardiac dysfunction (5,6).

Early detection of patients developing myocardial dysfunction is of paramount importance in patients undergoing systemic chemotherapy (7). Sequential imaging with echocardiography and serial measurement of some biomarkers are the most frequently used methods for detecting CV toxicity (8-10). Cardiac troponins have been found to be useful in early detection of chemotherapy induced cardiomyopathy (CIC) (7,9,11-13). However, standard assays underestimate small troponin elevations and high-sensitive assays are much better for detecting subtle elevations (14). On the other hand, data about reliability of high-sensitive troponin assays for predicting CIC are limited. In this study, we aimed to investigate the predictability of subtle troponin alterations after first dose of anthracycline chemotherapy, detected by high-sensitive assays to detect CIC in patients with BC treated by anthracyclines and/or trastuzumab.

METHODS

The study protocol was approved by the Çukurova University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee at its meeting dated 23.08.2013 (Meeting No: 22, Decision No: 7). The study was conducted at Çukurova University Faculty of Medicine with the participation of the Departments of Oncology, Cardiology, and Biochemistry. All procedures performed during the study were in accordance with the ethical standards of the institutional research committee and with the Declaration of Helsinki (15).

Patient Selection

Chemo-naïve patients newly diagnosed with breast cancer (BC) and admitted to our Oncology Department for systemic chemotherapy were prospectively enrolled in the study. All participants had normal baseline cardiac function.

A total of 43 patients were included in the study. Among them, 20 patients had HER-2 positive tumors. Patients without HER-2 overexpression (n = 23) received anthracycline-based chemotherapy consisting of doxorubicin and cyclophosphamide (AC). Patients with HER-2 positive disease received the same anthracycline-based chemotherapy regimen followed by trastuzumab according to institutional treatment protocols. During the study period, pertuzumab was not routinely available at our institution; therefore, HER-2–targeted therapy in this cohort consisted exclusively of trastuzumab-based regimens.

All patients received a standardized anthracycline regimen consisting of doxorubicin 60 mg/m² administered for four cycles, corresponding to a fixed cumulative dose of 240 mg/m². No patient received additional anthracycline cycles beyond this protocol.

Endocrine therapy was not administered during the chemotherapy period evaluated in this study. According to institutional treatment practice, endocrine therapy (tamoxifen or aromatase inhibitors) was initiated only after the completion of chemotherapy. Radiotherapy was not administered during the chemotherapy period evaluated in this study. According to institutional treatment protocols,

radiotherapy was planned only after completion of systemic chemotherapy when indicated.

Patients with significant anemia (hemoglobin <11 g/dL) or hypoalbuminemia (serum albumin <3.5 g/dL) were not included in the study. The overall performance status of the study population was good, with patients generally having ECOG performance status of 0–1.

At baseline, patients were comprehensively evaluated regarding disease stage, cardiovascular history, and physical examination findings. The presence of diabetes mellitus (DM), hypertension (HT), and tumor characteristics including estrogen receptor, progesterone receptor, and HER-2 status were recorded. Patients receiving systemic chemotherapy for either adjuvant or metastatic indications were eligible.

Renal function parameters were evaluated at baseline. No patient had advanced renal dysfunction (eGFR < 60 mL/min/1.73 m^2).

Standard 12-lead electrocardiography (ECG) was performed at baseline. During follow-up, ECG evaluation was performed when clinically indicated. No clinically significant arrhythmic events were recorded.

Table 1. Timing of visits evaluating cardiovascular function

Visit	Timing of the Visit
Screening Visit (0)	Before initiation of SC
First Visit (1)	4-12 hours after administration of first dose of SC
Second Visit (2)	After administration of fourth dose of SC
Third Visit (3)	At the sixth month of SC

SC: Systemic chemotherapy

Patients with a history of other malignancies, prior systemic chemotherapy or chest radiotherapy, structural heart disease, previous exposure to cardiotoxic agents, or baseline BNP levels ≥200 ng/L at screening were excluded from the study. No participant had documented coronary artery disease.

A screening visit was done for CV evaluation before treatment, which was followed by 3 more visits. The timing of visits is listed on Table 1. Patients were monitored for symptoms and signs of heart failure in each visit accompanied by transthoracic echocardiography (TTE) evaluation and measurement of biochemical markers. A combination of Adriamycin (60 mg/m^2) and cyclophosphamide (600 mg/m^2) therapy was administered to all patients and repeated for four times with 21-day intervals. Additional chemotherapy with trastuzumab was administered to HER-2 positive patients.

Transthoracic Echocardiographic Evaluation

Patients have undergone TTE in each visit. Echocardiography was performed by General Electric Vingmed US System Vivid S5 device. Standard chamber dimensions were measured to evaluate cardiac function. Ejection fraction (EF) was calculated according to modified Simpson's method (16). We also measured trans-mitral early atrial filling (E) and atrial contraction (A) waves by pulsed wave (PWD) Doppler at a sweep speed of 50 mm/sec. Mitral annular early atrial filling (e'), atrial contraction (a') and ventricular contraction (s') velocities at the mitral leaflet insertion points of septal and lateral left ventricular walls were measured by using tissue Doppler imaging (TDI) (17). All of the measurements were done by taking the average measurement of three consecutive beats. E/A, E/e' and e'/a' ratios were calculated in each patient.

Laboratory Tests

A 5 mL venous blood sample was obtained from each patient at every scheduled visit. Blood samples were centrifuged immediately and the resultant plasma was stored at -70°C. High-sensitive troponin T (hs-TnT), brain natriuretic peptide (BNP) and high-sensitive C-reactive protein (hs-CRP) markers were analyzed in these plasma samples. Plasma hs-TnT and BNP levels were measured by electrochemiluminescence immuno-assay (ECLIA) via Roche Cobas e411 system, whereas hs-CRP levels were measured by nephelometry via Beckman Coulter IMMAGE system.

Statistical Analysis

Statistical analysis was performed by IBM SPSS system (SPSS Inc, Chicago, IL). Patients were stratified according to 6-month BNP levels. Although the initial study design aimed to identify anthracycline-induced cardiomyopathy through comprehensive evaluation including echocardiography and tissue Doppler imaging, the low incidence of overt clinical cardiomyopathy led us to define patients with BNP levels ≥200 ng/L as having biomarker-defined cardiac stress, reflecting subclinical cardiac dysfunction (SCD group) rather than established cardiomyopathy; the remaining patients were considered as controls. Importantly, BNP elevation was not used to define overt cardiomyopathy but rather as a surrogate marker of increased ventricular wall stress and subclinical cardiac dysfunction. Numeric variables with normal distribution were compared by t-Test, whereas numeric variables without normal distribution were compared by Mann-Whitney-U (MWU) Test. Categorical variables were compared by chi-square test. Logistic regression analysis was performed to observe independent impact of variables on plasma BNP elevation. Receiver operating curve (ROC) analysis was performed to determine the cut-off values of hs-TnT levels for predicting 6th month BNP elevation. A p value less than 0.05 was considered as statistically significant.

RESULTS

A total of 43 women with BC were included in this study. All patients completed the planned four cycles of anthracycline therapy; therefore, the cumulative doxorubicin dose was identical (240 mg/m^2) across the study cohort. Of these patients, 8 of them had BNP levels higher than 200 ng/L at the 6th month follow-up visit and 2 of these 8 patients showed signs and symptoms of clinical heart failure. The demographic variables, baseline laboratory measurements and echocardiographic data of both groups are listed on Tables 2 and 3. The SCD group was significantly older than controls. Also, hs-TnT levels were significantly higher in the SCD group before CC; however, the measured hs-TnT levels in both groups were below cut-off values.

Table 2. Demographic variables of both groups

Variable	SCD Group N=8	Controls N=35	p value
Age (years)	63.3±8.0	50.3±11.7	**.006**
Diabetes mellitus (N, %)	3 (37.5)	5 (14.3)	.153
Hypertension (N, %)	3 (37.5)	5 (14.3)	.153
Metastatic disease (N, %)	4 (50.0)	14 (40.0)	.447
ER Positiveness (N, %) 8 (100)		27 (77.1)	.162
PR Positiveness (N, %)	7 (87.5)	24 (68.6)	.407
HER-2 Positiveness (N, %)	6 (75.0)	14 (40)	.100
Trastuzumab Use (N, %)	6 (75.0)	14 (40)	.100

SCD: Subclinical Cardiac Dysfunction, ER: Estrogen receptor, PR: Progesterone receptor

Table 3. Laboratory and echocardiographic variables at baseline

Variable	SCD Group N=8	Controls N=35	p value
hs-TnT$_0$ (ng/L)	9.81±3.70	6.27±3.01	**.022**
BNP$_0$ (ng/L)	110.95±64.39	73.78±51.95	.132
hs-CRP$_0$ (mg/L)	0.67±0.66	0.74±1.18	.748
EF$_0$ (%)	64.75±2.71	65.14±2.56	.963
E$_0$/A$_0$	1.92±0.54	1.10±0.34	.748
E$_0$/e$_0$'	7.27±1.94	7.81±1.40	.317
s$_0$' (cm/sec)	9.0±1.5	8.4±2.0	.317

SCD: Subclinical Cardiac Dysfunction, hs-TnT: high-sensitive Troponin-T, BNP: brain natriuretic peptide, hs-CRP: high-sensitive C-reactive protein, E/A: Early filling to left atrial contraction velocity ratio, E/e': Transmitral to annular early filling velocity ratio, s': annular systolic contraction velocity

Table 4. Laboratory and echocardiographic variables 4-12 hours after first dose of anthracycline chemotherapy

Variable	SCD Group N=8	Controls N=35	p value
hs-TnT$_1$ (ng/L)	28.72±39.76	9.00±4.51	**.013**
BNP$_1$ (ng/L)	211.8±168.5	67.6±61.27	**.020**
hs-CRP$_1$ (mg/L)	0.83±0.49	0.91±1.53	.317
EF$_1$ (%)	63.4±1.5	65.40±4.0	.140
E$_1$/A$_1$	1.06±0.32	0.93±0.97	.471
E$_1$/e$_1$'	7.57±2.10	7.65±2.10	.890
s$_1$' (cm/sec)	8.7±1.9	8.8±2.1	.863

SCD: Subclinical Cardiac Dysfunction, hs-TnT: high-sensitive Troponin-T, BNP: brain natriuretic peptide, hs-CRP: high-sensitive C-reactive protein, E/A: Early filling to left atrial contraction velocity ratio, E/e': Transmitral to annular early filling velocity ratio, s': annular systolic contraction velocity

The laboratory and echocardiographic parameters measured 4-12 hours just after first dose of anthracyclin containing chemotherapy are listed on Table 4. High-sensitive troponin-T and BNP levels were found to be higher in the SCD group when compared with control group. However, the echocardiographic parameters seemed similar in both groups.

Measurement of biochemical and echocardiographic variables after 4th dose of anthracycline containing chemotherapy and at 6th month of CC are listed on Tables 5&6. Brain natriuretic peptide levels were significantly higher in the SCD group as expected, however hs-TnT levels showed no significant alteration between groups. At 6th month follow-up, EF and systolic annular s' wave parameters were significantly impaired in the SCD group.

We have performed logistic regression analysis to see the independent influences of age, DM, HT, hs-TnT$_0$, hs-TnT$_1$ and BNP$_1$ variables on 6th month BNP elevation in women undergoing anthracycline containing chemotherapy (Hoshmer-Lemeshow goodness of fit p= 0.787). Only the parameters measured 4-12 hours after first dose of chemotherapy, hs-TnT$_1$ (OR: 1.154 (0.974-1.336 in 95 % CI) and BNP$_1$ (OR: 1.009 (1.001-1.018 in 95 % CI) showed a trend toward association with BNP elevation at 6 months. In the ROC analysis (Figure 1), hs-TnT$_1$ levels above 12.85 ng/L predicted 6th month BNP elevation with a sensitivity of 62.5 % and a specificity of 85.7 %. Furthermore, values higher than a cut-off value of 18.65 ng/L, predicted 6th month BNP elevation with a specificity of 97.1 %.

Table 5. Laboratory and echocardiographic parameters after 4th dose of anthracycline chemotherapy			
Variable	**SCD Group N=8**	**Controls N=35**	**p value**
hs-TnT$_2$ (ng/L)	13.23±9.58	14.64±6.08	.302
BNP$_2$ (ng/L)	1047.61±2080.53	64.81±49.60	**.000**
hs-CRP$_2$ (mg/L)	0.70±0.81	0.73±0.46	.364
EF$_2$ (%)	64.38±2.07	65.00±3.08	.679
E$_2$/A$_2$	1.13±0.58	1.04±0.34	.988
E$_2$/e$_2$'	8.39±2.61	7.61±2.57	.381
s$_2$' (cm/sec)	8.5±2.4	8.7±1.7	.240

SCD: Subclinical Cardiac Dysfunction, hs-TnT: high-sensitive Troponin-T, BNP: brain natriuretic peptide, hs-CRP: high-sensitive C-reactive protein, E/A: Early filling to left atrial contraction velocity ratio, E/e': Transmitral to annular early filling velocity ratio, s': annular systolic contraction velocity

Table 6. Laboratory and echocardiographic parameters at 6th month of systemic chemotherapy.			
Variable	**SCD Group N=8**	**Controls N=35**	**p value**
hs-TnT$_3$ (ng/L)	17.58±6.74	17.91±14.73	.274
BNP$_3$ (ng/L)	2304.91±3587.60	74.46±54.23	**.000**
hs-CRP$_3$ (mg/L)	2.29±3.94	0.76±1.28	.093
EF$_3$ (%)	58.75±5.42	64.59±3.55	**.004**
E$_3$/A$_3$	1.03±0.58	1.09±0.45	.433
E$_3$/e$_3$'	8.75±3.51	8.34±3.69	.550
s$_3$' (cm/sec)	7.7±3.1	8.9±1.8	**.028**

SCD: Subclinical Cardiac Dysfunction, hs-TnT: high-sensitive Troponin-T, BNP: brain natriuretic peptide, hs-CRP: high-sensitive C-reactive protein, E/A: Early filling to left atrial contraction velocity ratio, E/e': Transmitral to annular early filling velocity ratio, s': annular systolic contraction velocity

Given the limited number of HER2-positive patients receiving trastuzumab in our cohort, a subgroup analysis according to trastuzumab exposure was not statistically powered and therefore was not performed. This issue is acknowledged as a limitation of the study.

DISCUSSION

In this prospective study, we aimed to evaluate the predictive value of subtle troponin elevations for the development of cardiac dysfunction in 43 women with breast cancer undergoing systemic chemotherapy. Importantly, the cumulative anthracycline dose was standardized in the study (240 mg/m² for all patients), which eliminates cumulative dose variability as a potential confounding factor in the assessment of chemotherapy-related cardiac dysfunction. Although oestrogen receptor positivity was common in our cohort, endocrine therapy was not administered during the chemotherapy period evaluated in this study. Therefore, the potential cardiovascular effects of aromatase inhibitors or tamoxifen could not have influenced the cardiac biomarker measurements or the development of chemotherapy-related cardiac dysfunction in this cohort. Radiotherapy is a well-recognized contributor to long-term cardiac morbidity in breast cancer, particularly in patients receiving left-sided chest irradiation. However, none of the patients in the present cohort received radiotherapy during the study period in which cardiac biomarkers were assessed. Therefore, radiotherapy exposure could not have contributed to the observed cardiac outcomes. Potential confounding factors known to influence BNP levels, such as severe anaemia, hypoalbuminemia, or poor performance status, were minimized in the present cohort. Patients with haemoglobin levels below 11 g/dL or serum albumin

levels below 3.5 g/dL were excluded, and the overall performance status of the study population was ECOG 0–1.

Only two patients developed clinical signs of heart failure at 6 months. However, eight patients (18.6%) demonstrated a significant increase in BNP levels at the 6-month follow-up. We demonstrated that even subtle elevations of hs-TnT measured shortly after the first dose of anthracycline-containing therapy were associated with subsequent BNP elevation in this cohort. Moreover, hs-TnT levels measured 4–12 hours after the first chemotherapy dose predicted 6-month BNP rise with high specificity at a cut-off value of 18.65 ng/L. In the present study, early hs-TnT elevation showed a trend toward association with BNP elevation at 6 months in logistic regression analysis (OR: 1.154, 95% CI: 0.974–1.366). Although this association did not reach conventional statistical significance, hs-TnT demonstrated discriminatory capacity in the ROC analysis. This finding suggests that early myocardial injury detected by hs-TnT may precede later BNP elevation and subclinical cardiac dysfunction. The lack of statistical significance in regression analysis may be related to the relatively small sample size of the study cohort.

An important limitation of the present study is the relatively small number of cardiotoxicity events. With only eight SCD cases, the statistical power for multivariable logistic regression analysis is limited. Therefore, the regression results should be interpreted as exploratory and hypothesis-generating rather than definitive.

Importantly, BNP elevation does not by itself establish a diagnosis of cardiomyopathy; rather, it reflects increased ventricular wall stress and may represent early or subclinical cardiac dysfunction. In the present study, BNP was therefore used as a surrogate biochemical marker to identify patients at increased risk of developing chemotherapy-related cardiac impairment, particularly in a setting where overt clinical heart failure was infrequent. This biomarker-driven approach reflects a shift from late-stage cardiotoxicity detection toward early identification of myocardial stress, which is increasingly emphasized in contemporary cardio-oncology practice.

Cardiotoxicity is one of the most important complications of anthracyclines and trastuzumab, two drug classes widely used in breast cancer treatment (18). Cardiotoxic reactions may occur in acute, subacute, or chronic forms (6). Patients are traditionally monitored with transthoracic echocardiography (TTE) during and after chemotherapy. However, left ventricular ejection fraction (EF) is relatively insensitive for detecting early myocardial injury. Since systolic function is often preserved in the initial stages, acute and subacute cardiotoxicity may remain undetected by conventional TTE. A reduction in EF typically becomes evident only after structural myocardial damage has already occurred. In this context, biomarker-based approaches such as BNP and hs-TnT may provide earlier insight into evolving myocardial stress and injury before overt systolic dysfunction develops (18).

Adding Doppler and tissue Doppler measurements to TTE examination increases the probability of predicting the occurrence of SCD in the acute and subacute phases. Impairment of diastolic function is observed prior to systolic deterioration (19). A number of studies have shown that reduction of E/A wave ratio, an indicator of impaired diastolic function might be observed in early stages after CC administration and this impairment is a significant predictor of emerging CIC (20-22). Tissue Doppler measurements allow us to demonstrate subtle changes in diastolic functions. Annular to tissue early diastolic filling wave ratio (E/e') is a very good indicator of diastolic filling pressures and its increase might be associated with diastolic dysfunction (17,23). In this study, we have observed some alterations in diastolic functions in the follow-up period. There was no significant difference between SCD group and controls in terms of diastolic function measurements.

However, certain methodological limitations should be considered when interpreting these echocardiographic findings. One such limitation of

the present study is the absence of global longitudinal strain (GLS) assessment. Although GLS is currently recommended in cardio-oncology guidelines as a sensitive parameter for the early detection of subclinical cardiac dysfunction, the present study was conducted before strain imaging had become widely implemented in routine clinical echocardiographic practice in many centers. Therefore, cardiac function in our cohort was evaluated using conventional echocardiographic parameters, including LVEF and Doppler-derived indices.

There are a number of biomarkers useful for prediction, diagnosis and prognosis stratification of cardiac damage. Cardiac troponins are gold standard markers for demonstrating cardiac damage in almost all clinical conditions, including CIC (24). Lipshultz et al have shown that Troponin-T elevation has occurred in 30 % of patients receiving anthracycline containing regimen for lymphoblastic leukemia, which was correlated with increased mortality (25). Sawaya et al studied patients with BC and stated that detectable hs-TnT assay along with decrease in myocardial strain rate at 3rd month of chemotherapy were the most important predictors of SCD development at 6 months (7). Subtle elevations have been observed after first daunorubicin dose in an animal model searching high-sensitive troponin rise in daunorubicin administration; whereas more significant elevations have been demonstrated after 5th and 8th administrations. These elevations seemed to occur with a peak between 4-6 hours after drug administration and declined after 24 hours (26). On the other hand, in a study conducted in long-term survivors of childhood cancers, Pourier et al didn't find a significant relationship between high-sensitive troponin levels and development of SCD in children whom have undergone anthracycline treatment with an 8.3 years follow-up (27). However, they compared the values measured in routine follow-up visits, not in samples collected in true time intervals after drug administration. In our study, we found a significant relationship between 6th month BNP elevation and subtle elevations of hs-TnT levels measured 4-12 hours after the first dose of anthracycline containing therapy. On the other hand, high-sensitive troponin levels were almost similar between both groups in the samples collected at our 2nd and 3rd visits; just like results of Pourier's study.

Natriuretic peptides are important markers for diagnosis and risk stratification of heart failure (28). Various studies have demonstrated that persistent BNP elevation is associated with left ventricular dysfunction in patients receiving anthracyclines (29-31). In our study, BNP levels were significantly increased in the SCD groups in all visits performed after drug administration as expected. Another marker important for risk stratification in this patient population, hsCRP, didn't show any significant difference in both groups in our study.

The most important limiting factor in our study is low number of patient population. Since we had limited number of patients, clinical heart failure occurred in only 2 of our patients. Because of this, we set up the primary endpoint as 6th month BNP elevation. Eight of our patients showed progressive BNP elevation in 6 months; whereas the BNP levels were stable in the others.

Another point to consider is that dual HER-2 blockade with pertuzumab was not routinely available during the study period at our institution. Consequently, patients with HER-2 positive disease received trastuzumab-based therapy only. The absence of pertuzumab should therefore be taken into account when interpreting the cardiac outcomes of this cohort.

Although some patients in our cohort had metastatic breast cancer, these cases were limited to bone metastases and did not represent extensive visceral tumour burden. Additionally, none of the patients demonstrated severe anaemia or clinically significant hypoalbuminemia that could independently influence BNP levels. Nevertheless, the inclusion of patients with different treatment intents (adjuvant, neoadjuvant, and metastatic settings) represents a potential source of heterogenity. Due to the relatively small sample size, subgroup analyses according to treatment intent were not

feasible and this should be considered a limitation of the present study.

In conclusion, early hs-TnT elevation following the first dose of anthracycline chemotherapy may help identify patients at risk of subsequent ventricular stress, as reflected by persistent BNP elevation. These findings suggest that early biomarker surveillance could play a role in detecting subclinical cardiotoxicity before the development of measurable systolic dysfunction or overt clinical heart failure. However, given the exploratory nature and limited sample size of the present study, these results should be interpreted cautiously. Larger prospective studies integrating biomarker kinetics with advanced imaging parameters and clinical outcomes are needed to confirm these findings and to establish a more comprehensive risk prediction model for chemotherapy-related cardiac dysfunction.

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Conflict of Interest

The authors declare that they have no conflict of interests regarding content of this article..

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Ethical Declaration

The study protocol was approved by the Çukurova University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee at its meeting dated 23.08.2013 (Meeting No: 22, Decision No: 7).

Is previously presented?

Portions of the data presented in this manuscript have been previously presented in scientific meetings. Part of the study was presented as a poster at the ESC Congress 2015 (London, UK, August 29–September 2, 2015). Additionally, some of the data were presented as an oral presentation at the 18th International Eastern Mediterranean Family Medicine Congress (April 25–28, 2019).

These presentations represent preliminary dissemination of the data, and the current manuscript includes a more comprehensive analysis and full dataset

Is drived from thesis?

This manuscript is derived from the author's medical specialty thesis entitled "Prospective Evaluation of Cardiotoxicity Using Serological and Non-Invasive Methods in Patients Receiving Antineoplastic Chemotherapy", completed at Çukurova University Faculty of Medicine as a medical specialty thesis in 2015.

Authorship Contributions

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Scientific Reports in Medicine

Research Article

Causes of maternal mortality and the effectiveness of healthcare services: a retrospective analysis in Adana province

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Abstract

Objective: This study aims to retrospectively analyze maternal deaths occurring in Adana province between 2011 and 2016, evaluating the causes of death, demographic and clinical characteristics, and access to healthcare services.

Method: A total of 105 maternal death cases were analyzed. The majority of the cases were married, had low education levels, and were covered by the Social Security Institution or the "Green Card" system. Syrian refugees accounted for 9.5% of maternal deaths, with partial differences observed in their access to healthcare services.

Result: The majority of maternal deaths resulted from direct (34.3%) and indirect (50.5%) causes. It was determined that the number of consultations with an obstetrician was higher in direct maternal deaths and lower in coincidental deaths. The cesarean section rate was high (72.4%), and deaths predominantly occurred during the postpartum period (72.4%). Most deaths took place in tertiary healthcare institutions, with an increase in mortality rates observed during shift hours.

Conclusion: To reduce maternal mortality, it is recommended to strengthen primary healthcare services, control cesarean section rates, and develop more inclusive health policies for refugees. This study provides significant data for determining policies to prevent maternal mortality and increasing the effectiveness of healthcare services.

Keywords: Maternal death, Mortality, Refugee, Health Care, Pregnancy, Public Health

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INTRODUCTION

It is a fundamental right for every woman to experience a healthy pregnancy and childbirth process and to receive the necessary support during this period. Maternal mortality is a critical indicator of a society's overall health and welfare level and reflects the quality of women's health services. Maternal death is defined as the death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management (1).

The World Health Organization (WHO) and its partner organizations have published a historic consensus text and strategy document to end preventable maternal deaths. The primary goal set in this document is to reduce the global maternal mortality ratio to less than 70 per 100,000 live births by 2030 (2). Turkey is among the countries that have achieved this goal. Although the maternal mortality rate in Turkey has shown a downward trend in recent years, it remains at significant levels. In Turkey, 12.6 mothers lose their lives per 100,000 live births (3).

Most maternal deaths are preventable, with the most common causes including hemorrhage (37%), infections (22%), and preeclampsia/eclampsia (14%) (4). Early diagnosis and timely access to effective treatment can prevent pregnancy-related complications. The objective is to increase social awareness, continue the training of the community and healthcare professionals, and maximize the quality of healthcare services (5).

As part of the program implemented by the Ministry of Health of the Republic of Turkey starting in 2007, all maternal deaths occurring throughout the country have been meticulously reported, and each case has been evaluated in detail by scientific commissions established at the provincial and national levels according to the World Health Organization's three-degree delay model.

Due to the civil war that started in Syria in 2011, people who were forced to migrate from the country began to seek refuge in Turkey. By 2016, the number of Syrian refugees in Turkey reached 2,800,000, with approximately 224,000 of them residing in Adana (6). Refugee women face difficulties accessing healthcare in every country, and this affects maternal mortality and morbidity (7).

The aim of this study is to determine the causes of pregnancy-related deaths in Adana between 2011 and 2016, based on the total number of live births and maternal deaths in the last 5 years.

METHOD

All pregnancy-related deaths occurring in health institutions under the responsibility of the Adana Provincial Health Directorate between January 1, 2011, and December 31, 2016, were examined retrospectively. In our study, causes of death were categorized according to the International Classification of Diseases, 10th Revision (ICD-10) codes.

The definition of pregnancy-related death is the loss of life due to causes directly or indirectly related to pregnancy, regardless of the cause of death, within 42 days of the termination of pregnancy. This definition includes not only sudden and underlying causes of death, but also factors such as anemia, pregnancy or childbirth-related complications, and serious maternal morbidity that may have contributed to death.

Maternal Mortality Rate is estimated per 100,000 live births and is calculated by dividing the number of maternal deaths by 100,000.

* Direct maternal deaths are defined as obstetric complications resulting from interventions, omissions, incorrect treatment, or a chain of events resulting from any of the above.

* Indirect maternal deaths are classified as deaths resulting from previous existing disease or disease that developed during pregnancy and which was not due to direct obstetric causes, but which was aggravated by the physiological effects of pregnancy.

However, the physiological effects of pregnancy can worsen the situation. Maternal deaths are

defined as the death of a woman during pregnancy, childbirth, or within 42 days after childbirth due to obstetric causes directly or indirectly related to pregnancy, childbirth, or the puerperium. Late maternal deaths are defined as deaths occurring between 42 days and one year after childbirth.

These deaths are not considered work-related. To classify a maternal death as preventable, at least one degree of preventability probability involving patient, family, nurse, facility, system, and/or societal factors is required. If at least one identifiable change in these factors exists, the death is considered preventable.

Permission to collect data was obtained from healthcare facilities under the responsibility of the Adana Provincial Health Directorate within the scope of the research.

Data were analyzed using descriptive statistical methods. SPSS 22.0 (SPSS Inc., Chicago, IL, USA) was used for data analysis. Findings are presented as frequency, percentage, and descriptive summary statistics. Chi-Square or Fisher's Exact tests were employed for comparing categorical variables.

The procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000.

RESULT

Among the 105 cases analyzed, 95.2% were married and 4.8% were single. 90.5% were citizens of the Republic of Turkey, while 9.5% had Syrian refugee status. Regarding education, 48.6% of the cases had a primary school education or lower.

* Clinical Indicators: 58.1% of the cases had a Body Mass Index (BMI) between 25-30. Autoimmune diseases (8.6%), diabetes (8.6%), and a history of infertility (13.3%) were observed. The cesarean section rate was remarkably high at 72.4%. Hypertension is absent in 76.2% of cases. The rate of cases with rare blood types is 6.7%. The rate of multiple pregnancies is 5.72%.

* Timing and Location: 72.4% of deaths occurred in the postpartum period. 61.9% of deaths took place during shift hours (evenings and weekends). The highest number of deaths occurred on Friday (19%), and the lowest number of deaths occurred on Tuesday (4.8%). 74.3% of maternal deaths were brought to the hospital by ambulance, and 1.0% by private vehicle. In 64.8% of deaths, the cause of death was consistent with the diagnosis at admission. Tertiary health institutions accounted for approximately 80% of total maternal deaths.

* Access to Care: In direct maternal deaths, the average number of visits to an obstetrician during pregnancy was 7.8, compared to 7.0 in indirect deaths and 3.4 in coincidental deaths ($p < 0.05$).

Maternal deaths were classified as direct (34.3%; n=36), indirect (50.5%; n=53), and accidental (15.2%; n=16). The mean age in direct maternal deaths was 32.7, in indirect maternal deaths 30.2, and in accidental maternal deaths 24.9. The age difference between the groups was statistically significant ($p=0.002$).

No statistically significant difference was found between height, body weight, BMI, gravida, and parity and maternal deaths. The postpartum period was 7.4 days on average in direct maternal deaths, 12.8 days in indirect maternal deaths, and 11.9 days in accidental maternal deaths (statistically significant).

In direct maternal deaths, the average number of visits to the gynecologist during pregnancy was 7.8. This number was 7.0 in indirect maternal deaths and 3.4 in accidental maternal deaths. A statistically significant relationship was found between the number of gynecological visits and maternal deaths ($p<0.05$).

In direct maternal deaths, the average number of visits to the family physician from the 28th week of pregnancy onwards was 4.6. This value was found to be 4.5 in indirect maternal deaths and 2.5 in accidental maternal deaths. The lower number of visits to the family physician in accidental maternal deaths was found to be statistically significant

($p<0.05$).

In addition, the average number of gynecological visits to the pregnant woman before her death was 3.3 in direct maternal deaths, while this number was 3.0 in indirect maternal deaths and 1.9 in accidental maternal deaths. This difference is statistically significant ($p=0.047$).

This study evaluated the differences in health indicators and demographic characteristics between Syrian refugees and Turkish citizens. Overall, no statistically significant differences were found between the two groups in terms of many parameters. However, significant differences were observed in some parameters such as the number of visits to an obstetrician during pregnancy, the number of visits to different obstetricians, and stillbirth weeks. These findings indicate significant differences in access to and utilization of healthcare services, and further research is needed in this area.

This study also examines the distribution and significant differences of various demographic and clinical variables at different levels of healthcare. These findings can help understand demographic and clinical differences in healthcare delivery and contribute to the development of health policies. While maternal deaths in primary care institutions consist only of Turkish citizens, maternal deaths in secondary and tertiary healthcare institutions also include Syrian refugees. Maternal deaths among Syrian refugees are particularly concentrated in secondary healthcare facilities. The distribution between nationality and healthcare institution is not random, indicating that policies regarding access to healthcare services need to be evaluated.

No patient transfers were made to primary care institutions (85.7%), ambulance use was low (14.3%), and no use of private vehicles was observed (0%). In transfers to secondary and tertiary care institutions, ambulance use was quite high (80% and 78.3%), the rate of cases where no transfer was made was lower (20% and 20.5%), and the use of private vehicles was rare (0% and 1.2%).

In primary care settings, the vast majority of deaths occurred outside the healthcare facility (85.7%), while the rate of deaths occurring within the healthcare facility was low (14.3%). In secondary and tertiary healthcare facilities, all deaths occurred within the healthcare facility (100%).

In primary care settings, the vast majority of deaths occurred during pregnancy (85.7%), while the mortality rate during the postpartum period was lower (14.3%). In secondary and tertiary healthcare settings, deaths mostly occurred during the postpartum period (66.7% in secondary care and 78.3% in tertiary care), while the mortality rate during pregnancy was lower (33.3% in secondary care and 21.7% in tertiary care).

No significant differences were found between healthcare levels among the following variables: marital status ($p=0.790$), education level ($p=0.114$), social security ($p=0.344$), BMI ($p=0.546$), autoimmune disease ($p=0.403$), history of diabetes ($p=0.625$), history of infertility ($p=0.371$), hypertension status ($p=0.877$), rare blood group ($p=0.336$), multiple pregnancy ($p=0.946$), mode of delivery ($p=0.817$), diagnosis causing death ($p=0.723$ and $p=0.116$), time of death ($p=0.167$), and time of postpartum maternal death ($p=0.775$). The distribution of these variables was similar across institutions. Although maternal deaths occurred at different rates in different time periods, these differences were not statistically significant. This indicates that maternal deaths occur at similar rates during nighttime, working hours, and evening periods. Therefore, there is insufficient evidence to say that maternal deaths are more or less frequent during any given time period.

There is no statistically significant difference in the distribution of nationality and maternal deaths according to time periods. For both Turkish citizens and Syrian refugees, deaths occur at similar rates during night, working hours, and evening hours. This indicates that there is insufficient evidence to say that deaths are more frequent or less frequent in any given time period. Similarly, there is no

statistically significant difference in the distribution of institutional and maternal deaths according to time periods. In primary, secondary, and tertiary care institutions, deaths occur at similar rates during night, working hours, and evening hours. This also reveals that there is insufficient evidence to say that deaths are more frequent or less frequent in any given time period.

DISCUSSION

This study examines maternal mortality in Adana province in detail, considering demographic, clinical, and healthcare access aspects. The findings of this study, when compared with international literature, contribute to understanding the strengths and weaknesses of the current state of maternal health in Turkey.

Demographic and Clinical Factors:

Consistent with WHO data, low socioeconomic status and low education levels remain significant risk factors (1). This study found that a large proportion of maternal deaths occurred among individuals with low levels of education, and 9.5% were Syrian refugees. Similarly, studies in Europe and America show that immigrant women experience difficulties accessing healthcare services, and this is a factor that increases maternal mortality (8, 9).

Health Status and Pregnancy Complications:

When clinical factors associated with maternal deaths are examined, chronic diseases such as hypertension and diabetes are seen to play a significant role. The literature reports that diseases such as gestational diabetes and preeclampsia are among the main causes of maternal mortality (4). Hypertension was absent in 76.2% of the cases, while diabetes was present in 8.6% in this study. However, it should be emphasized that obesity is a significant risk factor, as a large proportion of the cases were in the overweight category in terms of Body Mass Index. Obesity is a significant factor that increases cesarean section rates and raises the risk of postpartum complications (10).

Delivery Method and Maternal Mortality:

In our study, the cesarean section rate was found to be quite high (72.4%). Although the WHO recommends a cesarean section rate of 10-15%, cesarean births are increasing in many countries (2). Previous studies have shown that cesarean section rates are also high in Turkey and that this situation may be related to maternal mortality (11). Cesarean births can increase the risk of maternal death, especially due to postoperative complications.

Maternal Mortality Types and Access to Healthcare:

When maternal deaths were classified as direct, indirect, and accidental, our study found that indirect maternal deaths were the most frequent (50.5%). Similarly, indirect deaths constitute a large portion of maternal mortality in developed countries, but direct deaths are more common in developing countries (12). Considering the factor of access to healthcare, the number of prenatal check-ups was found to be related to the types of maternal death. Previous research has indicated that inadequate prenatal care particularly increases indirect maternal deaths (13).

In our study, it was observed that a large proportion of maternal deaths were concentrated in tertiary healthcare facilities. This finding suggests that, as shown in previous studies, high-risk pregnancies are generally referred to better-equipped centers (9). However, it was found that the vast majority of maternal deaths, especially those occurring in primary healthcare facilities, took place outside of hospitals. The literature also indicates that primary healthcare services need to be strengthened and that early intervention plays a critical role in reducing maternal mortality (5).

Syrian Refugees and Access to Healthcare Services:

There may be differences in access to healthcare services for Syrian refugee women. International literature also indicates that refugee women have less access to prenatal care services and therefore carry

a higher risk of maternal mortality (14). However, our study found no statistically significant difference in maternal mortality between Syrian refugees and Turkish citizens. This suggests that the healthcare services provided by Turkey to its refugee population may be effective. Nevertheless, the differences in some parameters (number of gynecologist visits, week of delivery, etc.) indicate the need for further research to improve access to healthcare services for women in this group.

Time of Death and Healthcare Services:

IT was found in this study that maternal deaths most frequently occurred during the postpartum period (72.4%) and were particularly concentrated within the first 42 days after delivery. Literature states that the postpartum period is the most critical period for maternal mortality and that women should be closely monitored during this time (15). Furthermore, it was found that the times of death largely coincided with shift hours (61.9%). This finding indicates that the adequacy of healthcare services during shift hours should be questioned. Previous studies have shown that maternal deaths occurring during shift hours may be related to increased workload, limited specialist staff, and lack of resources (16).

Service Delivery and Timing: The concentration of deaths in tertiary centers suggests that high-risk pregnancies are correctly referred to equipped centers, but it also highlights the critical nature of these cases. The fact that 61.9% of deaths occurred during shift hours warrants an investigation into the adequacy of specialist staffing and resource availability during these periods (16).

A civil war in a region leads to refugee migration, affecting the public health of neighboring countries. It does this by impacting maternal mortality, which is a key indicator of the development of health systems. This study has shown us this.

Conclusion

The findings of this study are largely consistent with the international literature. However, some strategies need to be developed to reduce maternal mortality:

* Strengthening Primary Care: Enhancing prenatal care for early detection of high-risk pregnancies.

* Optimizing Shift Services: Ensuring adequate specialist staff during night and weekend shifts.

* Controlling Cesarean Rates: Encouraging cesarean sections only when medically necessary.

* Inclusive Refugee Policies: Developing targeted policies to facilitate access to prenatal care for refugee women.

* Improved Monitoring of Maternal Health Data: Data collection processes related to maternal deaths should be improved, and risk factors should be analyzed more thoroughly.

In conclusion, this study presents important findings regarding maternal mortality in Adana and, when compared with similar studies in the international literature, demonstrates the need to improve health policies for maternal health in Turkey. Increasing access to healthcare services and early detection of high-risk pregnancies are crucial for reducing maternal mortality.

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Conflict of Interest

The authors declare that they have no conflict of interests regarding content of this article..

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Ethical Declaration

Ethical permission was obtained from the Çukurova University, Medical Faculty Clinical Research Ethics Committee for this study with date 07.10.2016 and number 24, and Helsinki Declaration rules were followed to conduct this study.

Authorship Contributions

Concept: MS, Design: MS, Supervising: FİU, Financing and equipment: Data collection and entry: MS, FİU, Analysis and interpretation: MS, FİU, Literature search: MS, Writing: MS, FİU, Critical review: MS

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Research Article

Investigation of the relationship between air quality and health outcomes in Bilecik, Türkiye: A descriptive ecological study

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Abstract

Objective: To evaluate temporal trends in air quality indicators and their ecological-level associations with respiratory and cardiovascular hospital admissions in two districts of Bilecik Province between 2020 and 2024.

Method: This ecological, retrospective study used annual district-level data from two public hospitals and two fixed air-monitoring stations in Bilecik city center and Bozüyük. Annual mean concentrations of $PM_{2.5}$, $PM_{2.5}$, SO_2, NO_2, O_3 and CO were obtained from routine monitoring records. Hospital admissions were classified using ICD-10 codes for major respiratory and cardiovascular conditions. Descriptive trends were examined, and ecological co-variation between pollutants and total respiratory/cardiovascular admissions was assessed using Spearman's rank correlation ($p<0.05$).

Results: $PM_{2.5}$ levels declined in both districts, whereas $PM_{2.5}$ concentrations increased and remained higher in Bozüyük. Respiratory and cardiovascular admissions decreased in 2020–2021 and rose again from 2022 onwards. At the district–year level, respiratory admissions were positively correlated with $PM_{2.5}$'in Bozüyük and negatively correlated in the city center, while NO_2 showed negative correlations in both districts. Cardiovascular admissions were positively correlated with $PM_{2.5}$ and temperature, whereas $PM_{2.5}$ showed a negative association, particularly in Bozüyük.

Conclusion: Air quality indicators and hospital admissions displayed distinct temporal and spatial patterns across the two districts, with a stronger $PM_{2.5}$ burden and clearer ecological associations in Bozüyük, the more industrialized and traffic-intense district. Although not implying individual-level causality, the findings provide policy-relevant evidence supporting prioritization of $PM_{2.5}$-focused monitoring, emission-control measures, and integration of environmental indicators into local health-surveillance systems in medium-sized industrial regions.

Keywords: air pollution; $PM_{2.5}$; respiratory diseases; cardiovascular admissions; ecological study

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1. INTRODUCTION

Air pollution is recognized as one of the leading environmental determinants of population health worldwide. According to the World Health Organization (WHO), ambient air pollution is responsible for an estimated 4.2 million premature deaths annually, mainly due to cardiovascular and respiratory causes (1). Evidence from the Global Burden of Disease (GBD) study indicates that fine particulate matter ($PM_{2.5}$) contributes substantially to morbidity and mortality, accounting for approximately 12% of the global burden attributable to major chronic diseases (2). In addition, multi-country modelling studies have shown that increases in ambient $PM_{2.5}$ concentrations are associated with higher all-cause mortality at the population level (3).

A growing body of epidemiological and meta-analytical evidence indicates that long-term exposure to $PM_{2.5}$, PM_{10}, NO_2, SO_2 and O_3 is associated with adverse health outcomes, particularly chronic respiratory and cardiovascular diseases (4-6). Previous reviews have reported increased risks of COPD, asthma exacerbations, acute myocardial infarction and lung cancer among populations chronically exposed to particulate matter and traffic-related pollutants (5-8). Although substantial reductions in SO_2 and PM_{10} emissions have been reported in parts of Europe, recent assessments suggest that population exposure to $PM_{2.5}$ and NO_2 remains above recommended thresholds in many regions (9).

In Türkiye, air quality assessments indicate that a large proportion of the population continues to be exposed to pollutant concentrations exceeding WHO guideline values, particularly with respect to $PM_{2.5}$ (10). However, most available studies have focused on major metropolitan areas such as Istanbul, Ankara and Bursa, whereas evidence from small-to-medium sized industrial provinces remains limited. This gap is particularly relevant for regions where industrial activities and transport corridors coexist with residential settlements, but where long-term ecological evaluations are scarce.

Bilecik is a medium-sized province in north-western Türkiye characterized by industrial production, mining activities and varying topographic and meteorological conditions across its districts. The provincial centre and Bozüyük district differ considerably in terms of traffic load, industrial density and urban structure, providing a meaningful context for comparative ecological assessment. Building on previous work linking long-term air pollution exposure to cardiopulmonary outcomes this study evaluates five-year air pollutant trends alongside hospital admission profiles (7,8).

Accordingly, this ecological study aimed to examine the relationship between annual average concentrations of selected ambient air pollutants (PM_{10}, $PM_{2.5}$, SO_2, NO_2 and O_3) and hospital admissions for predefined respiratory and cardiovascular disease groups in two districts of Bilecik Province between 2020 and 2024.

Specifically, the study pursued the following sub-objectives: (i) to evaluate five-year trends in ambient air pollutant concentrations in the selected districts, (ii) to compare air pollutant profiles between Bilecik city center and the industrial district of Bozüyük, and (iii) to explore district-level correlations between annual pollutant concentrations and hospital admission indicators for respiratory and cardiovascular diseases.

Rather than establishing causal inference at the individual level, the study seeks to provide a district-level descriptive assessment that may support local environmental health monitoring and contribute to evidence-informed policy development in medium-sized industrial provinces.

2. METHODS

2.1. Study design

This ecological and retrospective epidemiological study covered the years 2020–2024 and evaluated district-level variation in annual air pollutant concentrations and hospital admission profiles in Bilecik Province. Analyses were conducted at the district–year level, using annual averages of

environmental indicators and annual counts of hospital admissions as the unit of observation. The study included data from two public hospitals and two fixed ambient air monitoring stations.

The study does not aim to establish individual-level causal associations; rather, it provides a population-level descriptive assessment of the co-variation between air quality indicators and health service utilization.

2.2. Study location

This study was conducted in Bilecik, a province in the Southern Marmara Region of Türkiye, with an estimated population of 228,000 in 2024.[11] The province is characterized by industrial activity, mining sites and a semi-continental climate, with winter months marked by reduced air circulation and temperature inversion conditions that may increase pollutant accumulation.

Two districts with contrasting structural characteristics were included:

(1) Bilecik city center, located in a basin-like topography with lower traffic density and fewer large-scale industries, and

(2) **Bozüyük**, situated along the D650 transportation corridor with higher industrial density and freight traffic.

The primary health data sources were Bilecik Training and Research Hospital (city center) and Bozüyük State Hospital (industrial district), both of which serve as referral centers and maintain comprehensive electronic admission records.

2.3. Air quality and meteorological data

Annual mean concentrations of particulate matter (PM_{10}, $PM_{2.5}$), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), ozone (O_3) and carbon monoxide (CO) for 2020–2024 were obtained from the Bilecik Provincial Directorate of Environment, Urbanization and Climate Change. Data from two fixed monitoring stations (Bilecik Merkez and Bozüyük) were used.

Hourly measurements were screened using station-level quality-control flags. Valid hourly records were aggregated to daily means and then to **annual averages per station**, consistent with the ecological design.

Meteorological data were obtained from the same authority. In line with the annual aggregation structure, **only annual mean temperature** was used as a contextual variable; other meteorological indicators (e.g. humidity, wind speed/direction) and seasonal stratification were not included.

2.4. Health data

Health data were retrospectively retrieved from hospital admission records for 2020–2024 through the Bilecik Provincial Directorate of Health, using the International Classification of Diseases, 10th Revision (ICD-10) codes. Disease groups were defined as a priori based on conditions frequently reported in the literature as being sensitive to long-term air pollution exposure. Respiratory and cardiovascular diagnoses constituted the primary analytical focus, while selected cancer and allergic disease groups were examined descriptively. Relevant ICD-10 subcodes were included for each group (Table 1).

Data included daily emergency and outpatient admissions. Because the dataset reflects routine health-service utilization, repeated admissions for the same patient on different dates may be present and were retained as an indicator of service burden. Duplicate technical entries (identical patient ID, diagnosis and timestamp) and inter-facility transfer records were excluded.

2.5. Data preparation

Separate datasets (hospital admissions, air pollutants and meteorological variables) were harmonized into a unified district–year structured database. Air pollutant and temperature variables were expressed as annual means.

Table 1. Disease groups and ICD-10 codes used in the study		
Disease group	**ICD-10 codes**	**Description**
Acute bronchitis	J20, J20.8, J20.9	Acute bronchitis and unspecified subtypes
Asthma	J45.*	Asthma and allergic/intrinsic subtypes
COPD	J44.*	Chronic obstructive pulmonary disease
Pneumonia	J15–J18	Bacterial, viral and unspecified pneumonia
Respiratory failure	J96.*	Acute, chronic and unspecified respiratory failure
Rhinitis	J30.0–J30.4	Allergic and vasomotor rhinitis
Lung cancer	C34.*	Malignant neoplasms of bronchus and lung
Skin cancers	C43–C44	Melanoma and other skin cancers
Bladder cancer	C67.*	Bladder cancer
Allergic conditions	T78.0–T78.4	Anaphylaxis and allergic reactions
Dermatitis	L20–L30	Atopic and contact dermatitis
Myocardial infarction	I21	Acute myocardial infarction
Heart failure	I50	Heart failure
Hypertension	I10–I15	Hypertension

2.6. Ethical considerations

The research was approved by the KTO Karatay University Faculty of Medicine, Non-Drug and Non-Medical Device Research Ethics Committee (Date: 26/12/2024; Approval No: 2024/018). Institutional permissions were granted by the Provincial Health Directorate and the Provincial Directorate of Environment, Urbanization and Climate Change. The study was conducted in accordance with the principles of the **Declaration of Helsinki.** All data were anonymized prior to analysis, and no individual-level identifying information was used.

2.7. Statistical analysis

Analyses were performed using SPSS for Windows, version 18.0 (SPSS Inc., Chicago, IL, USA). Numerical variables were assessed for distributional characteristics using visual (histograms, Q–Q plots) and analytical (Kolmogorov–Smirnov) methods.

Between-district differences in annual mean pollutant concentrations were examined using the independent samples t-test. Year-to-year variation within districts was assessed using one-way ANOVA for parametric variables. Hospital admissions were summarized as annual counts and rates by disease group and district. To explore population-level co-variation between environmental indicators and health service utilization, Spearman correlation coefficients were calculated between annual mean pollutant concentrations and annual respiratory and cardiovascular admission indicators. A two-tailed p-value <0.05 was considered statistically significant.

3. RESULTS

Between 2020 and 2024, annual average concentrations of major air pollutants showed distinct spatial and temporal patterns across the two districts. PM_{10} levels exhibited a decreasing trend in both districts, whereas $PM_{2.5}$ concentrations increased over time, with a more pronounced rise in Bozüyük. Mean annual concentrations of PM_{10}, $PM_{2.5}$ and NO_2 were consistently higher in Bozüyük compared with the city centre throughout the study period. While SO_2 levels declined markedly in the city centre, a fluctuating pattern was observed in Bozüyük. Annual mean temperature remained higher in the city centre in all study years (Table 2).

The distribution of hospital admissions by disease group demonstrated a noticeable decline during the early pandemic period (2020–2021), followed by a gradual increase from 2022 onwards. This pattern was observed for both respiratory and cardiovascular disease groups in both districts, with the post-pandemic rise being more evident in 2023–2024.

These changes likely reflect not only epidemiological variation but also shifts in healthcare-seeking behaviour over the pandemic and post-pandemic phases (Table 3).

Table 2. Descriptive statistics of air quality variables by year and station

Air quality parameters	Location	Years					p**
		2020	2021	2022	2023	2024	
PM_{10}	Center	30,02	27,34	22,22	23,27	24,27	**<0,001**
	Bozüyük	57,43	51,24	44,33	44,23	43,77	**<0,001**
	p*	**<0,001**	**<0,001**	**<0,001**	**<0,001**	**<0,001**	
$PM_{2.5}$	Center	9,09	11,92	12,16	14,66	14,63	**<0,001**
	Bozüyük	21,27	20,90	19,31	24,62	25,52	**<0,001**
	p*	**<0,001**	**<0,001**	**<0,001**	**<0,001**	**<0,001**	
SO_2	Center	6,31	4,23	5,46	2,54	2,18	**<0,001**
	Bozüyük	6,27	6,67	10,34	11,08	8,53	**<0,001**
	p*	0,892	**<0,001**	**<0,001**	**<0,001**	**<0,001**	
NO	Center	11,02	4,90	9,27	7,85	5,39	**<0,001**
	Bozüyük	22,84	21,35	20,11	19,75	21,54	0,452
	p*	**<0,001**	**<0,001**	**<0,001**	**<0,001**	**<0,001**	
NO_2	Center	8,84	15,44	29,09	18,62	10,72	**<0,001**
	Bozüyük	23,13	24,58	26,32	20,70	32,72	**<0,001**
	p*	**<0,001**	**<0,001**	**0,002**	**0,004**	**<0,001**	
O_3	Center	58,26	53,00	51,08	40,36	43,72	**<0,001**
	Bozüyük	59,92	38,66	29,89	29,52	58,32	**<0,001**
	p*	0,679	**<0,001**	**0,011**	**<0,001**	**<0,001**	
Temperature	Center	13,75	13,34	13,01	14,11	14,65	**0,043**
	Bozüyük	12,19	12,00	11,48	12,65	13,05	0,072
	p*	**0,007**	**0,022**	**<0,001**	**0,009**	**0,006**	

Annual average values for air quality parameters are given. *Independent simple t test; **One-Way ANOVA

When district-year level ecological associations were examined, total respiratory admissions showed a **positive correlation with $PM_{2.5}$ in Bozüyük and a negative correlation in the city centre**, alongside a negative correlation with NO_2 in both districts. The strength of the association between $PM_{2.5}$ and respiratory admissions was greater in Bozüyük, where a concurrent positive correlation with temperature was also observed. Correlations with PM_{10} were weaker and of smaller magnitude. Total cardiovascular admissions demonstrated a positive correlation with $PM_{2.5}$ and temperature in both districts. In addition, a strong negative correlation was observed between cardiovascular admissions and PM_{10} in Bozüyük, whereas a moderate negative association was present in the city centre. Correlations with NO_2 were weaker and less consistent across districts (Table 4).

4. DISCUSSION

The present ecological study revealed notable temporal and spatial differences between the two districts of Bilecik in terms of both air quality indicators and hospital admissions over the period 2020–2024. Consistent with national emission inventories and regional assessments from other industrial provinces in Türkiye, PM_{10} levels showed a declining trend in both districts (9,12,13). This pattern likely reflects the combined impact of emission control measures in stationary sources, improvements in residential fuel quality and temporary reductions in traffic-related emissions

during the early pandemic period. The downward trend in PM_{10} therefore appears to be partly policy-linked, suggesting that long-term emission control strategies may have yielded measurable improvements in coarse-particle exposure.

Table 3. Distribution of health visits by year and hospital location

Type of disease	Location	Years				
		2020	2021	2022	2023	2024
Acute bronchitis	Center	422	761	186	554	2391
	Bozüyük	1063	330	966	1485	857
Asthma	Center	3119	2768	1681	1640	1967
	Bozüyük	3226	2431	2194	3806	3689
COPD	Center	1909	2087	1721	2594	2319
	Bozüyük	2769	1216	1527	2099	2427
Pneumonia	Center	4019	2791	1251	834	746
	Bozüyük	3762	1675	1790	2818	2867
Respiratory failure	Center	87	109	39	55	36
	Bozüyük	184	181	243	320	382
Rhinitis	Center	6350	7989	7976	11808	12124
	Bozüyük	4054	3148	5846	10237	5596
Lung cancer	Center	74	72	72	140	97
	Bozüyük	17	14	40	64	73
Skin cancers	Center	3	11	4	187	331
	Bozüyük	5	8	20	103	62
Bladder cancer	Center	119	172	90	93	138
	Bozüyük	55	62	44	4	3
Allergic conditions	Center	3301	4513	3808	4503	5330
	Bozüyük	2456	3324	3141	3842	3164
Dermatitis	Center	217	262	283	330	474
	Bozüyük	185	219	320	279	271
Myocardial infarction	Center	193	79	153	294	450
	Bozüyük	676	697	396	340	328
Heart failure	Center	814	900	1031	1386	1037
	Bozüyük	1166	1310	1182	879	1330
Hypertension	Center	12692	10601	14242	21545	25649
	Bozüyük	8505	6817	9486	10274	12876

The total number of applications for diseases is given annually.

In contrast, $PM_{2.5}$ concentrations increased over the study period, with higher and more persistent levels observed in Bozüyük. This divergence between PM_{10} and $PM_{2.5}$ trends is in line with international evidence indicating that, although reductions in coarse particles may be achieved through technological and regulatory measures, fine particulates remain strongly influenced by combustion processes, secondary aerosol formation and mixed industrial sources. (1,14,15). In mid-sized industrial settlements such as Bozüyük, where freight transport and industrial activity are more pronounced, these mechanisms may contribute to a sustained $PM_{2.5}$ burden, even in the presence of reductions in PM_{10}.

The temporal distribution of hospital admissions also reflected pandemic-related dynamics. Both respiratory and cardiovascular admissions declined

in 2020–2021 and increased again from 2022 onwards, consistent with hospital-based studies from Türkiye and international literature reporting fluctuations in respiratory hospitalizations in relation to changes in air pollution levels and healthcare utilization patterns during and after the pandemic (16,17). This pattern likely represents the combined effect of reduced healthcare attendance in the early pandemic phase and the resumption of routine care and mobility in later years, underlining the importance of interpreting environmental health indicators within their broader social and service-delivery context.

Table 4. Correlation between key air pollutants and total respiratory / cardiovascular admissions at the district–year level (2020–2024)

Pollutant / Variable	Respiratory total r (p)	Cardiovascular total r (p)
Merkez		
PM_{10}	**0,980** (<0.001)*	**–0.551** (<0.001)
SO_2	**0.430** (<0.001)	**–0.653** (<0.001)
NO	0.136 (0.130)	0.054 (0.547)
NO_2	**–0.897** (<0.001)	0.143 (0.109)
$PM_{2.5}$	**–0.777** (<0.001)	**0.774** (<0.001)
O_3	**0.777** (<0.001)	**–0.774** (<0.001)
Temperature	0.128 (0.153)	**0.690** (<0.001)
Bozüyük		
PM_{10}	**0.211** (0.001)	**–0.858** (<0.001)
SO_2	**–0.211** (0.001)	**0.626** (<0.001)
NO	**0.397** (<0.001)	**–0.235** (<0.001)
NO_2	**–0.526** (<0.001)	**0.264** (<0.001)
$PM_{2.5}$	**0.497** (<0.001)	**0.673** (<0.001)
O_3	**0.397** (<0.001)	**–0.235** (<0.001)
Temperature	**0.497** (<0.001)	**0.673** (<0.001)

r values represent the Spearman correlation coefficient.

At the district–year level, total respiratory admissions showed a positive correlation with $PM_{2.5}$ in Bozüyük and a negative correlation in the city centre, while NO_2 was negatively associated with respiratory admissions in both districts. These results should be interpreted in light of pollutant mixtures and local emission profiles rather than as single-pollutant effects. Nevertheless, they remain broadly compatible with previous reviews and regional studies demonstrating that particulate-matter exposure is associated with increased hospitalizations for asthma, COPD and acute bronchitis at the population level (16,17). In this context, the stronger and directionally positive $PM_{2.5}$ association in Bozüyük may reflect the higher industrial and traffic-related exposure burden in this district. By contrast, the negative association observed in the city centre should not be interpreted as indicating a causal or protective effect. Instead, it may reflect ecological characteristics of the dataset, including concurrent temporal trends in both pollutant concentrations and healthcare utilization, as well as other contextual factors such as population mobility and healthcare-seeking behaviour during the study period. Because the analysis relied on annual aggregated indicators, inverse correlations may arise from overlapping temporal patterns rather than a direct causal relationship. Therefore, the observed negative relationship should be interpreted cautiously as a population-level association within the limitations of the ecological study design.

Similarly, total cardiovascular admissions were positively correlated with $PM_{2.5}$ and temperature

in both districts, while PM_{10} showed a negative association, particularly in Bozüyük. The positive association with $PM_{2.5}$ is consistent with ecological and time-series evidence linking fine particulate exposure with cardiovascular morbidity through pathways such as systemic inflammation, oxidative stress and endothelial dysfunction (18,19). The negative association with PM_{10}, by contrast, likely reflects the relative decline of coarse-particle emissions over time in parallel with the increasing dominance of $PM_{2.5}$, rather than a protective effect of PM_{10} itself. The stronger associations observed in Bozüyük may therefore be interpreted in terms of its higher industrial intensity and pollutant burden. In addition, recent analyses have highlighted the modifying role of ambient temperature on respiratory and cardiovascular morbidity, supporting the descriptive association observed in the present study (20).

Taken together, the findings of this study indicate patterns of co-variation between air quality indicators and major disease-group admissions at the ecological level, rather than individual-level causal effects. The heterogeneity across districts and years suggests that local emission characteristics, climatic factors and healthcare-seeking behaviour may modulate the strength and direction of associations. Even so, the parallel rise in $PM_{2.5}$ concentrations and the stronger ecological associations observed in Bozüyük provide context-specific, policy-relevant evidence emphasizing the need to prioritize fine-particulate monitoring and control strategies in medium-sized industrial provinces.

5. CONCLUSION

This five-year ecological analysis demonstrates that air quality indicators and major respiratory and cardiovascular admissions exhibit distinct temporal and spatial patterns across two districts with differing industrial and traffic characteristics. While PM_{10} levels declined, $PM_{2.5}$ concentrations increased — particularly in Bozüyük — where higher pollutant levels coincided with stronger district-level associations with healthcare utilization. Although the results do not imply causality at the individual level, they highlight the importance of strengthening $PM_{2.5}$-focused monitoring, integrating environmental indicators into local health-surveillance systems and supporting targeted environmental–public-health policies in mid-sized industrial regions.

6. LIMITATIONS

This study has several limitations that should be considered when interpreting the findings. First, the ecological design does not allow individual-level exposure assessment, and therefore causal relationships between air pollution and health outcomes cannot be established. Second, air pollution exposure was estimated using annual mean concentrations from fixed monitoring stations, which may not fully capture intra-district variability or individual exposure differences. Third, hospital admission data reflect healthcare utilization rather than true disease incidence and may have been influenced by changes in healthcare-seeking behavior, particularly during the COVID-19 pandemic period. Finally, because the analyses were conducted using annual aggregated data, seasonal variations and short-term exposure effects could not be evaluated. Despite these limitations, the study provides a district-level overview of air quality and health indicators in a medium-sized industrial province where long-term environmental health evaluations remain limited.

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Conflict of Interest

The authors declare that they have no conflict of interests regarding content of this article..

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Ethical Declaration

This study was approved by the KTO Karatay University Faculty of Medicine Non-Drug and Medical Device Research Ethics Committee (IRB: 26.12.2024-018). Subsequent permissions were obtained from the Bilecik Provincial Health Directorate and the Bilecik Provincial Directorate of Environment, Urbanization and Climate Change.

Authorship Contributions

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Scientific Reports in Medicine

Case Report

Refractory thrombocytopenia after 177Lu-PSMA therapy: bone marrow infiltration (myelophthisis) versus treatment toxicity

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Abstract

Lutetium is a radiopharmaceutical used effectively to treat metastatic castration-resistant prostate cancer (mCRPC). Myelosuppression can occur after lutetium therapy, and it can be difficult to distinguish between treatment-related toxicity and bone marrow infiltration (myelophthisis), especially in patients with extensive bone metastases.

A 60-year-old male patient with metastatic castration-resistant prostate cancer was scheduled for 177Lu-PSMA therapy after progression on docetaxel and abiraterone. Thrombocytopenia developed after the first course. At the same time, the patient developed infective endocarditis. Although platelet counts temporarily improved with infection management, severe thrombocytopenia recurred after the second 177Lu-PSMA cycle.

Bone marrow biopsy revealed infiltration by prostate adenocarcinoma. It was determined that the patient's thrombocytopenia was caused by cancer infiltration of the bone marrow and the resulting myelophthisis.

Hematologic toxicity is a recognized complication of 177Lu-PSMA therapy in patients with mCRPC and extensive skeletal involvement, bone marrow is essential to differentiate between effects caused by treatment and myelophthisis in cases of refractory cytopenia.

Keywords: Lutetium, Myelophthisis, Prostate cancer, Thrombocytopenia.

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INTRODUCTION

Thrombocytopenia is a common hematological complication in cancer patients. Patients with cancer may develop thrombocytopenia for a variety of complex reasons. The most common causes of thrombocytopenia are systemic treatments, myelophthisis (marrow infiltration), tumor metastasis to the liver and spleen, liver failure, microangiopathic disorders such as disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, or hemolytic uremic syndrome, infection, graft versus host disease, and other drugs (1).

Myelophthisis is a form of bone marrow failure resulting in anemia, thrombocytopenia, neutropenia, and pancytopenia of different severities. It happens when abnormal tissue replaces bone marrow precursor cells and their stroma, usually due to metastatic carcinomas. This condition generally appears in the later stages of the disease. The primary tumors most often linked to myelophthisis are solid cancers like lung, breast, and prostate cancers (2).

Prostate cancer includes a range of biological, clinical, and molecular characteristics. Metastatic castration-resistant prostate cancer (mCRPC) is characterized by disease progression despite androgen deprivation therapy (ADT). Recently, radioligand therapy (RLT) targeting the type II transmembrane glycoprotein prostate-specific membrane antigen (PSMA) has emerged as a new treatment option for patients whose disease is refractory to docetaxel and androgen receptor pathway inhibitors. Lutetium-177 (177Lu)-PSMA-617 delivers beta-particle radiation to PSMA-expressing cells and their surrounding microenvironment. Multiple retrospective and prospective studies have shown that 177Lu-PSMA-617 exhibits strong anti-tumor activity and is well tolerated in patients with mCRPC (3, 4).

In Lu-PSMA therapy, myelosuppression can be a dose-limiting factor. In the VISION study, approximately 25% of patients experienced significant (grade 3) hematological adverse events, including anemia in 68 patients (12.9%), leukopenia in 13 patients (2.5%), and thrombocytopenia in 42 patients (7.9%). Risk factors for myelosuppression during radionuclide therapy include bone malignancies, existing hematologic impairments, prior myelotoxic treatments, the activity dose per cycle, and treatment duration (5). In PSMA-RLT, bone marrow is identified as a tissue at risk, which may limit the amount of medication that can be given and its effectiveness. When cancer spreads to the bone marrow, hematological reserves may decrease. Due to insufficient bone marrow, patients may be unable to their current cytoreductive therapy, increasing the risk of disease progression (6). Deciding if myelosuppression is caused by treatment or disease progression can be difficult. The best approach to managing mCRPC with significant bone marrow involvement remains uncertain.

CASE REPORT

A 60-year-old male patient presented in May 2019 with nocturia and dysuria. His PSA level was measured at 4.9 ng/mL. The histopathological analysis of the prostate biopsy confirmed adenocarcinoma, with a Gleason Score of 9 (5+4). PSMA-PET/CT identified several bone metastases. The patient was started on maximum androgen blockade with goserelin and bicalutamide. Due to the extensive disease, he received six cycles of docetaxel (75 mg/m^2) and prednisone (10 mg/day) beginning in October 2019. By December 2020, his PSA level began to increase, indicating castration-resistant disease. Later, he was treated with abiraterone (1,000 mg/day), 10 mg/day prednisone, and denosumab, which led to a clinical response. In March 2021, he developed myocardial angina, resulting in the discontinuation of abiraterone.

By May 2021, the patient showed disease progression, including bone pain, radiographic progression, and increased PSA levels. Restaged 68Ga-PSMA PET/CT images are shown in Figure 1. Large, widespread PSMA-avid bone lesions were detected with 68Ga-PSMA PET/CT, with a maximum SUV of 47.34. The PSA level was 75 ng/mL.

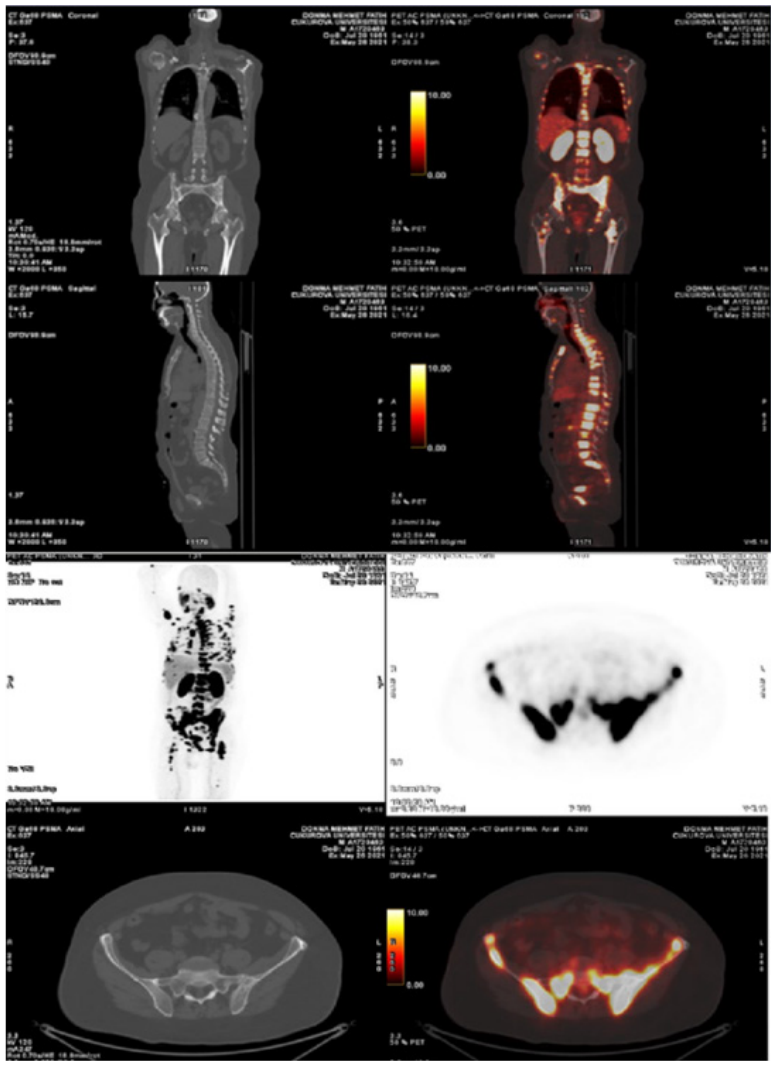

Figure 1: Restaged 68Ga-prostate-specific membrane antigen (PSMA) positron emission tomography (PET)/computed tomography (CT) images

Due to the high PSMA uptake in the bone lesions, the patient was treated with 177Lu-PSMA. Prior to treatment, the patient's laboratory parameters included a hemoglobin level of 9.9 g/dL, hematocrit of 28.5%, a platelet count of 105×10^9/L, and a white blood cell (WBC) count of 8.8×10^3/μL (neutrophils: 6.3×10^3/μL) (**Table 1**). In June 2021, following the first cycle of 177 Lu-PSMA therapy (200 mCi), the patient was hospitalized four days later due to fever. Laboratory evaluation showed a decline in hematological markers: hemoglobin 8.4 g/dL, hematocrit 24%, and platelets 63×10^9/L. Peripheral blood smear confirmed thrombocytopenia alongside anisocytosis and normochromic normocytic red blood cells. During this period, the patient developed mitral valve infective endocarditis, initially treated with meropenem and vancomycin. Following mitral valve replacement surgery, the antibiotic regimen was adjusted to daptomycin and fluconazole. After six weeks of therapy, laboratory values stabilized, with hemoglobin rising to 10.1 g/dL and platelets to 102×10^9/L. In August 2021, the patient, who showed improvement in laboratory parameters and overall clinical condition, received the second dose of 177 Lu-PSMA treatment (200 mCi). Ten days post-treatment, the patient presented with petechiae on the lower extremities and trunk. Laboratory tests confirmed severe thrombocytopenia with a platelet count of 5×10^9/L (**Figure 2**), while hemoglobin (10 g/dL) and WBC (4.2×10^3/μL). Peripheral

blood smear findings were consistent with the hemogram, showing no signs of hemolysis. Other biochemical parameters were largely within normal limits, including AST (40 U/L), ALT (15 U/L), total bilirubin (0.48 mg/dL), LDH (241 U/L), and creatinine (0.98 mg/dL). The patient had no history of heparin exposure, and inflammatory markers were low (procalcitonin: 0.17 ng/mL). Despite platelet transfusion, platelet levels did not increase.

Table 1: Laboratory Parameters During Treatment Course

Parameter (Unit)	Prior to Treatment	Post 1st Cycle	Prior to 2nd Cycle	Post 2nd Cycle
Hemoglobin(g/dL)	9.9	8.4	10.1	10.0
Hematocrit (%)	28.5	24.0	30.5	30
Platelets (x10^9/L)	105	63	102	5
White Blood Cells (x10^3/µL)	8.8	6.6	9.6	4.2
Neutrophils (x10^3/µL)	6.3	5.6	7.3	1.3

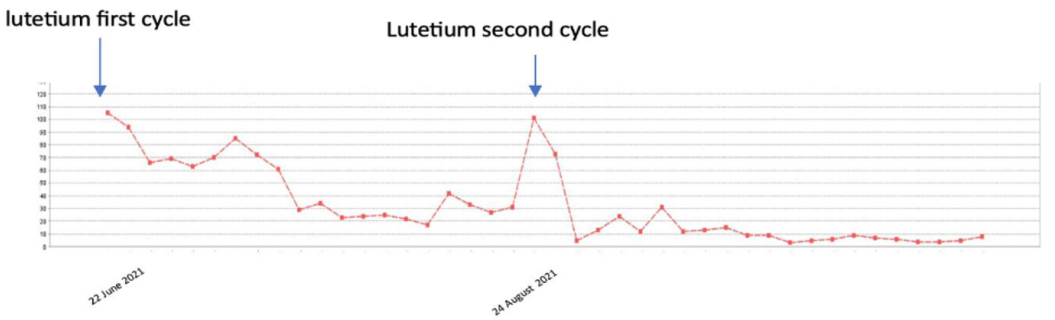

Figure 2: Platelet levels after lutetium therapy

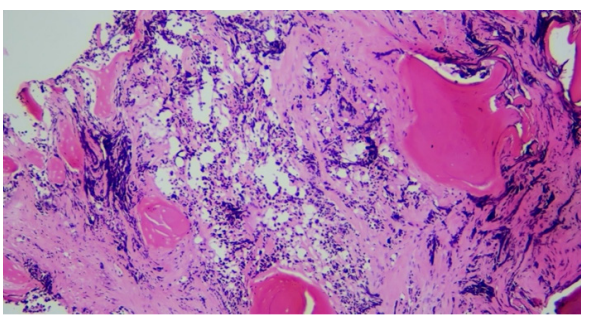

Figure 3A: Bone marrow biopsy, metastatic prostate carcinoma hematoxylin-eosin x200.

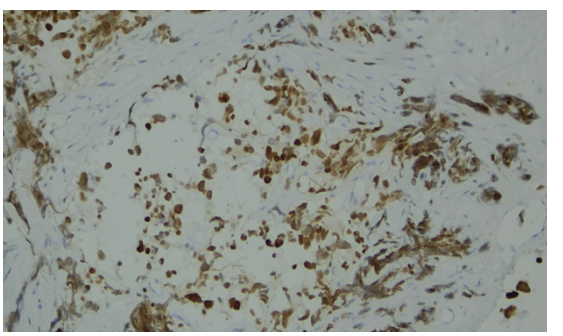

Figure 3B: Immunohistochemical stain NKX3.1 shows nuclear staining in tumor cells x200.

A biopsy and bone marrow aspiration were performed. Histopathologically, tumor clusters with extensive crush attenuation, large hyperchromatic nuclei, prominent nucleoli in some areas, eosinophilic cytoplasm, and glandular-structure-like areas were observed. (Figure 3A) Normal hematopoietic lineages, including megakaryocytes, were significantly depleted or obscured by the extensive fibroblastic activity and tumor infiltration, consistent with the patient's clinical thrombocytopenia. Immunohistochemical staining was used to determine the primary origin of the adenocarcinoma. The immunohistochemical staining of the biopsy revealed neoplastic cells that

were positive for keratin and NKX3.1 (Figure 3B) but negative for cytokeratin CK7, CK20, PSA, ERG, P63, TTF1, HMWK, Chromogranin, and sinaptofizin, indicating that cancer had spread to the prostate. During follow-up, the patient developed neutropenia and anemia. The patient died of neutropenic fever and sepsis.

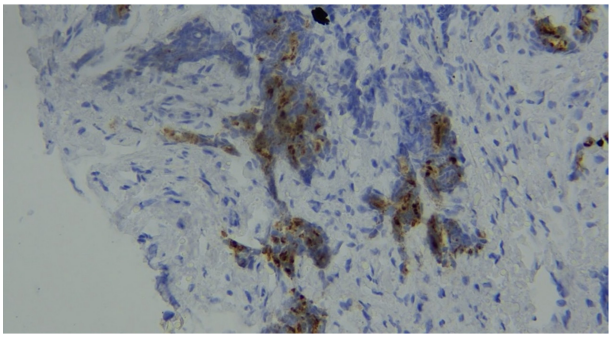

Figure 4: Immunohistochemical staining of the primary prostate biopsy specimen showing focal cytoplasmic PSA expression in neoplastic glandular structures (PSA, x200).

DISCUSSION

Myelophthisis is a rare and serious clinical problem that affects men with prostate cancer. When the disease spreads to the bone marrow, patients' hematological reserves may become compromised, potentially preventing them from receiving current cytoreductive therapy and increasing their risk of disease progression (7). In radionuclide therapy, blood-driven recirculating ß-irradiation and scatter radiation from bone metastases can cause or worsen myelosuppression (6). The use of RLT in this patient population has recently been studied retrospectively in a small number of trials. The findings of a study assessing the hematological safety of radioligand therapy with 177Lu-PSMA-617 in metastatic castration-resistant prostate cancer suggest that multiple cycles of RLT with 177Lu-PSMA-617 can be administered with acceptable rates of myelosuppression, with cytopenia being most often reversible, especially in earlier stages of disease progression (7). Platelet levels may normalize three to four months after PSMA-RLT treatment (8).

When there is a heavy burden of bone malignancies, previous chemotherapy with taxane-based drugs, or early stages of hematologic deterioration, significant new hematological adverse effects may appear (7). Our patient previously underwent treatment with docetaxel. Following that, he responded well to abiraterone treatment, but myocardial angina prevented the patient from completing the course of medication. In the third line lutetium therapy was administered. In a study that compared the effectiveness of Lu-PSMA treatment in patients with bone metastases based on the extent of bone involvement, the patients' survival showed a negative correlation with the degree of bone involvement. Response rates to therapy in patients with more than 20 bone lesions and widespread bone and bone marrow involvement were similar to those in the low-involvement group. However, it was found that these patients experienced higher rates of anemia and thrombocytopenia due to their treatment (9). Research examining potential links between hematological toxicity and treatment response in patients receiving PSMA-RLT found that patients with severe bone involvement and no post-treatment biochemical response experienced all grade 3 and 4 adverse events. (10) Our patient had multiple risk factors, including previous docetaxel treatment and widespread metastases in both the axial and appendicular skeleton.

In our patient, infectious endocarditis following the initial lutetium treatment complicated the cause of thrombocytopenia. The bone marrow biopsy was initially avoided because of the active infection and the improvement of cytopenia after treating the infection. However, after the second lutetium dose, thrombocytopenia recurred, and since there were no signs of new infection or toxic triggers, a bone marrow biopsy was performed. The biopsy confirmed the infiltration of prostate adenocarcinoma (myelophthisis) in addition to bone marrow fibrosis.

Table 2: Adverse Drug Reaction Probability Scale (Naranjo Algorithm)				
	Yes	**No**	**Do not know**	**Score**
1. Are there previous conclusive reports on this reaction?	+1	0	0	0
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	+2
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	0
4. Did the adverse reaction reappear when the drug was readministered?	+2	-1	0	+2
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	-1
6. Did the reaction reappear when a placebo was given?	-1	+1	0	0
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	0
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	0
				Total score= 3

The immunohistochemical staining of the biopsy revealed neoplastic cells that were positive for keratin and NKX3.1 (Figure 3B) but negative for cytokeratin CK7, CK20, PSA, ERG, P63, TTF1, HMWK, Chromogranin, and Synaptophysin. The loss of PSA expression in the metastatic marrow lesion, despite its positivity in the primary tumor biopsy, is a significant finding. PSA is considered a highly specific marker for detecting metastases of prostate tumors, but its sensitivity is limited due to decreased or lost expression in higher-grade or metastatic tumors, making additional markers necessary. Pathologically, although PSA (Figure 4A) and NKX3.1 tested positive when applied immunohistochemically to the patient's first biopsy sample—where he was initially diagnosed with prostate adenocarcinoma—PSA was negative in the tumor that metastasized to the bone marrow, although NKX3.1 was positive. In the literature, the detection rate of prostate origin of metastasis for single markers was 100% for NKX3.1 and 80.8% for PSA. Therefore, it is emphasized that combining PSA with NKX3.1 demonstrates higher sensitivity (11). While PSA is highly specific for prostatic tissue, its expression is known to diminish or disappear in poorly differentiated and metastatic lesions. Recent large-scale tissue microarray studies have demonstrated that up to 15-20% of advanced castration-resistant cases exhibit partial or complete loss of PSA immunoreactivity. (12) Furthermore, in the setting of bone marrow metastasis, NKX3.1 has been shown to be a more robust and sensitive marker than PSA, maintaining positivity even when PSA is negative (13).

The Naranjo Adverse Drug Reaction (ADR) scale was used to assess the causal relationship between lutetium treatment and the development of refractory cytopenia. The clinical scenario resulted

in a Naranjo score of 3, indicating a 'possible' causal relationship between the radiopharmaceutical treatment and hematological toxicity in our patient (14). These findings suggest that, although underlying myelophytosis is the main factor, the treatment may have worsened bone marrow depletion.

Additionally, the presence of bone marrow fibrosis in this case highlights a rare but important consequence of metastatic prostate cancer adenocarcinoma. Due to tumor metastasis to the bone marrow, anemia and thrombocytopenia caused by fibrosis are typical (15). Causes of death due to marrow fibrosis include complications from progressive bone marrow failure, portal or pulmonary hypertension, infections, thrombosis, and bleeding (16).

CONCLUSION

Radionuclide therapies are an effective option for patients with metastatic castration-resistant prostate cancer (mCRPC) and are typically well tolerated. However, myelosuppression, especially in patients with extensive bone metastases, is the most critical and dose-limiting factor during treatment. Distinguishing treatment-related hematologic toxicity from bone marrow infiltration (myelophthisis) is crucial for clinical management. Bone marrow biopsy is essential for differential diagnosis. Our case highlights the significance of myelophthisis and the diagnostic value of bone marrow biopsy in patients who develop refractory cytopenia after lutetium therapy.

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The authors declare that they have no conflict of interests regarding content of this article..

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Scientific Reports in Medicine

Case Report

Lamotrigine-induced DRESS syndrome in a patient with mood disorder and NAGS deficiency: A case report

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Abstract

N-acetyl glutamate synthase (NAGS) deficiency is a very rare autosomal recessive metabolic disease that affects the urea cycle and can cause serious morbidity and mortality. In these cases, mood disorders are rare, and potential side effects are important in the treatment of neurological and psychiatric conditions occurring due to the existing enzyme deficiency. In this study, a case of NAGS deficiency, epilepsy, and mood disorder, as well as drug rash with eosinophilia and systemic symptoms (DRESS) syndrome after lamotrigine use, is presented.

Keywords: N-acetyl glutamate synthase deficiency, DRESS syndrome, Lamotrigine, Mood disorder, Treatment

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INTRODUCTION

Urea Cycle Disorders (UCD) are rare inherited metabolic conditions that impair the efficiency of the urea cycle responsible for the removal of excess ammonia from the body (1). The rarest of UCDs, N-acetyl glutamate synthase (NAGS) deficiency, which was first described in 1981, is an autosomal recessive disorder caused by a homozygous or compound heterozygous mutation in the NAGS gene on chromosome 17q21 17q21.31, with an incidence of less than 1:2 000 000 (2,3). Infants with UCDs with complete enzyme deficiency often present in the neonatal period with hyperammonemic coma and symptoms related to hyperammonemia (4). In neonatal cases, malnutrition or feeding intolerance, vomiting, lethargy, hypertonia and/or hypotonia, seizures and tachypnea, and in later-onset cases, confusion or disorientation, vomiting, behavioral changes, ataxia, lethargy, decreased levels of consciousness, seizures, and hypotonia are among the most common symptoms (5,6). Patients with partial urea cycle enzyme deficiencies with late-onset symptoms may present with chronic encephalopathy, autism, learning disabilities, hyperactivity and self-destructive behaviors, vomiting with changes in level of consciousness, stroke-like attacks, as well as psychiatric symptoms such as episodic psychosis, bipolar disorder, and/or major depression in young people and adults as emphasized in previous studies[1]. It was reported that 47% of patients enrolled in the UCD consortium in the United States of America (USA) were diagnosed with an intellectual disability, 38% were diagnosed with learning disabilities, 20% were diagnosed with attention deficit and hyperactivity disorder (ADHD), and 3% were diagnosed with autism (7). In these patients, mood disorders are rare, and potential side effects are important in the treatment of neurological and psychiatric conditions associated with the existing enzyme deficiency8. Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a life-threatening delayed drug hypersensitivity reaction which is rare in childhood and has not been previously reported in patients with NAGS deficiency. DRESS syndrome is a reaction to certain drugs, especially anticonvulsant drugs, usually manifested by fever, generalized body rash, and increased eosinophil counts, but its most prominent feature is the systemic response seen in liver function, renal function, or other major organs (8).

In this study, we present a patient with NAGS deficiency, epilepsy, and mood disorder who developed lamotrigine-induced DRESS syndrome. This case highlights the potential vulnerability of individuals with underlying metabolic disorders to severe idiosyncratic drug reactions and underscores the importance of the early recognition and prompt discontinuation of the suspected agent to prevent life-threatening complications.

CASE

F 13-year-old female patient with known NAGS deficiency and epilepsy was referred to us by the pediatric metabolic diseases and nutrition outpatient clinic for mood lability.

It was learned that the patient was born with C/S, weighing 3200 grams. She started walking at 14 months of age, started talking at the age of 2.5 years, and completed toilet training at the age of 2.5 years. She was admitted to the emergency department on the 4th day after her birth with fever, feeding difficulties, and respiratory distress. Hyperammonemia was detected as a result of the tests performed, and she was hospitalized in the neonatal intensive care unit for 15 days with the pre-diagnoses of sepsis, metabolic syndrome, and encephalopathy. The results of the tests of the patient performed in the neonatal period are shown in Table 1. It was learned that the patient with high blood ammonia levels had been on a protein-restricted diet since the age of 6 years, and her blood ammonia levels by years are shown in Figure 1.

Table 1. Laboratory tests and treatment information of the patient

	Neonatal	Adolescent	DRESS
Symptoms	Feeding difficulty Dyspnea Fever Vomiting Lethargy	Convulsions Mood lability Decreased cognitive functions	Skin discoloration, Fever and spots, Enlarged pupil, constantly sleeping
Laboratory Tests	Ammonia: 296.3 (ref: 0-228) AST: 557 U/L (ref: 0-40) ALT: 326 U/L (ref: 0-41) CK: 1283U/L (ref<70) LDH: 5124U/L (ref: 160-500) Severely elevated: Glutamic acid Moderately elevated: Aspartic acid, Tyrosine Phenylalanine Mildly elevated: Serin, Ornithine, Lysine, Methionine, Leucine Liver NAGS enzyme activity: Could not be determined	Ammonia: 26.8 µmol/L (ref: 0-228) Arginine: 69.54 (ref: 45-125) Asparagine: 76.1 µmol/L (ref: 24.90) Phenylalanine: 62 µmol/L (ref: 38-180) Glycine: 421 µmol/L (ref: 149-417) Glutamate: 46.4 µmol/L (ref: 22-131) Glutamine: 518 µmol/L (ref: 333-809) Histidine: 57.28 µmol/L (ref: 41-106) Liver NAGS enzyme activity: Could not be determined	Hb: 12.6 g/dL (ref: 11.5-15), WBC: 5.98x10^3/uL (ref: 4.5-13), Lymphocytes: 0.64x10^3/uL (ref: 1-4.8). Eosinophils: 0.26x10^3/uL (ref: 0.02-0.5), Platelets: 121x10^3u/L (ref: 150-450), AST: 18 U/L (ref<25), ALT: 60 (ref<24), GGT: 43 U/L (ref<33), CK: 57 U/L (ref<145), CR: 0.63 mg/dL (ref: 0.57-0.87), Fibrinogen: 237.7 mg/dL (ref: 70-400), Complement C4: 5.37 mg/dL (ref: 16.00-38.00), Complement C3: 22.90 mg/dL (ref: 79.00-152.00), p-ANCA: negative c-ANCA: negative Anti-dsDNA: negative ANA: negative PCR: HHV 6, Mycoplasma pneumonia, CMV, EBV negative
Treatments	Blood glucose stabilization (approx. 150) Sodium benzoate Carnitine 200 mg/kg B vitamins Coenzyme Q Protein: starting from 0.5 g/kg raised to 2 g/kg Lipid: started at 0.5 g/kg.	Current Treatment Carglumic acid 3600 mg/day Clobazam 30 mg/day Aripiprazole 15 mg/day	Methylprednisolone 32 mg/day
Outcomes	15 days of hospitalization in neonatal intensive care. Advanced tests performed. Discharged after no ammonia elevation was found in her follow-ups.	Blood ammonia concentrations under control. Diagnosed with epilepsy at the age of 12. No epileptic seizures for 10 months. Decreased cognitive functions. Mood lability.	

ALT: Alanine Transaminase, AST: Aspartate Transferase, CK: Creatine Kinase, LDH: Lactate Dehydrogenase, Hb: Hemoglobin, WBC: White Blood Cell, GGT: Gamma Glutamyl Transferase, CR: Creatinine, ANCA: Antineutrophil Cytoplasmic Antibodies, Anti-dsDNA: Anti-Double-Stranded Deoxyribonucleic Acid, ANA: Antinuclear Antibody, PCR: Polymerase Chain Reaction, CMV: Cytomegalovirus, EBV: Epstein-Barr Virus, HHV-6: Human Herpesvirus 6

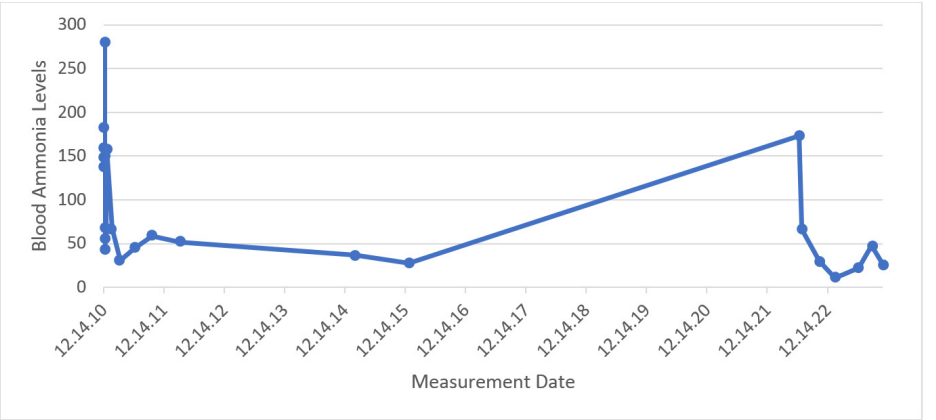

Figure 1. Blood ammonia changes.

The patient, who had no epileptic seizures in the first years of her life had a tonic-clonic seizure at the age of 11 years and was diagnosed with epilepsy, and medication was recommended. Again, at the age of 11, the patient was diagnosed with NAGS deficiency as a result of detailed genetic analysis. The parents of the patients were related, and there was no known metabolic or psychiatric disease in her family.

It was reported that the patient's mood fluctuated approximately every 15 days. During elevated periods, she talked excessively, displayed pressured speech, engaged in excessive spending, showed increased attention to self-care and heightened energy, required less sleep, demonstrated distractibility, and reported racing thoughts (consistent with DSM-5 hypomania criteria, including decreased need for sleep, distractibility, and flight of ideas) (9). Following these days, she had periods of locking herself in her room for a few days, burning incense, and meditating with music all day. During these periods, she no longer enjoyed activities she had previously found pleasurable, preferred to be alone, felt persistently tired, had difficulty falling asleep, struggled to study, and stated that she was unable to sustain her attention (these symptoms were consistent with DSM-5 criteria for a depressive episode, including loss of interest, fatigue, sleep disturbance, and impaired concentration) (9). These complaints had been going on for about 2 years.

Following a comprehensive psychiatric evaluation, the patient was diagnosed with Bipolar II Disorder in accordance with the DSM-5 diagnostic criteria (9).

Two years ago, she was brought to a child and adolescent psychiatrist, she was followed up with a diagnosis of anxiety disorder and received sertraline 100 mg/day for 6 months. Her enthusiasm and energy increased after the sertraline treatment, her family stopped the treatment thinking that she did not benefit from this treatment, and she had not used psychiatric drugs for the last 6 months. The patient had increased aggressive behaviors in the last 2 years and had 1 suicide attempt by wrapping a rope around her neck in 2023. Aripiprazole 5 mg/day was started, and the dose was increased to 10 mg/day after 1 week due to mood lability. Haloperidol 0.5mg/day was started simultaneously. When the patient was referred to us, she was on carglumic acid at 3600 mg/day for her metabolic diagnosis and clobazam at 30 mg/day for epilepsy. It was learned that the patient had tonic-clonic epileptic seizures every month since her first seizure at the age of 11. The patient, who could not use valproic acid (VA) as an anticonvulsant due to the risk of hyperammonemia, was prescribed lamotrigine 25 mg/day in addition to her ongoing treatment for epilepsy by the pediatric neurology clinic. On the 17th day of her lamotrigine treatment, it was learned that she was brought to the emergency department due to skin discoloration, fever and spotting, dilated pupils, and constant sleepiness, and as a result of further examinations and investigations, she was hospitalized in the pediatric allergy and immunology diseases inpatient clinic with the diagnosis of DRESS syndrome.

In 2024, the patient's Wechsler Intelligence Scale for Children-Revised (WISC-R) test revealed an overall intelligence score of 56, and the clinical observation result was "dull-normal intelligence". The results of the brain magnetic resonance imaging performed in 2020 were normal. Electroencephalography (EEG) performed in September 2024 provided normal results.

Clinical Outcome

The blood tests of the patient performed during the diagnosis of DRESS syndrome revealed thrombocytopenia in complete blood count (CBC), slightly elevated alanine aminotransferase (ALT) in liver function tests, normal blood urea nitrogen and creatinine in renal tests, Complement C4: 5.37 mg/dL (ref: 16.00-38.00), Complement C3: 22.90 mg/dL (ref: 79.00-152.00), and negative serum autoimmune antibodies. Human herpes virus 6, mycoplasma pneumonia, cytomegalovirus (CMV), and Epstein–Barr virus (EBV) were not detected. After the reaction, lamotrigine was discontinued, and 32 mg/day methylprednisolone was added to the treatment. The treatment results are presented in Table 1. The patient was hospitalized in the pediatric allergy and immunology inpatient clinic for 2 weeks after the reaction. She was brought to us for follow-up after her discharge. It was observed that nystagmus started in her eyes after the drug reaction. It was learned that she had been calmer and less irritable for the last 4 weeks, but the same complaints started again after lamotrigine was discontinued. During the examination of the patient, lisping was observed in her tongue, and haloperidol was discontinued considering that the condition was due to the haloperidol treatment. The patient is currently on aripiprazole 15 mg/day and is followed up by us at frequent intervals. She had experienced no seizures for 10 months, and her September 2024 EEG examination result was normal.

DISCUSSION

In this article, we present a patient diagnosed with hyperammonemia in the neonatal period, diagnosed with NAGS deficiency at the age of 11 years, had epilepsy and bipolar disorder, and developed DRESS syndrome due to lamotrigine use. To our knowledge, this is the first case report describing a patient with NAGS deficiency who developed DRESS syndrome secondary to lamotrigine. Most patients with NAGS deficiency present early in life, but cases of later onset have also been reported (6,10). In a review of 98 cases of NAGS deficiency reported until 2020, it was stated that 1 case was diagnosed prenatally, 57 cases were diagnosed in the neonatal period, 29 cases were diagnosed post-neonatally, and 5 cases were defined as late onset (6). The most common clinical symptoms in neonatal cases are feeding difficulties, vomiting, lethargy, coma, convulsions, hypertonia/hypotonia, and tachypnea. Common symptoms in later-onset cases include vomiting, confusion, ataxia, lethargy, seizures, and hypotonia (11). In our case, hyperammonemia was detected in the neonatal period, and respiratory distress, feeding difficulty, and vomiting symptoms were present. NAGS deficiency and epilepsy were diagnosed at the age of 11 years, and mood disorder was diagnosed at the age of 12.5 years. Diseases that cause hyperammonemia usually present as severe neurological metabolic problems in the neonatal period or in the first months of life, as in our patient. The patient in our case report was hospitalized in the intensive care unit at the age of 4 days with complaints of fever, moaning, respiratory distress, and feeding difficulties.

In a retrospective cross-sectional study investigating the neurological outcomes of UCD patients (5 cases of NAGS deficiency), the impact of peak ammonia levels and frequency of hyperammonemia episodes on neurological outcomes was emphasized, and patients with abnormal neurological parameters were reported to have a significantly higher mean number of annual episodes of hyperammonemia (12). All four participants (one child and three adults) with NAGS deficiency in a longitudinal study of the Urea Cycle Disorders Consortium (UCDC) performed within the average range of intellectual functioning, and one woman who was not diagnosed until adulthood

was reported to have experienced severe psychiatric problems and cognitive impairment prior to NAGS deficiency diagnosis and treatment (13). Intellectual, adaptive, and behavioral functioning may be impaired in children with UCDs. In a study characterizing the cognitive, adaptive, and emotional/behavioral functioning of 92 children with UCD (33 neonatal onset, 59 late onset), children presenting with neonatal onset were reported to have worse outcomes than those with onset times later in childhood, with about half of the children performing in the intellectual disability range, whereas even in children with late-onset UCDs, evidence of neurocognitive and behavioral impairment was seen, especially in terms of attention and executive functions (4). In the intelligence assessment of our case, a dull-normal level of intelligence was determined. In a review summarizing neuropsychological outcomes among patients with eight types of UCDs (including NAGS deficiency) in reports published from 1980 to 2019, data on cognitive abilities of 1649 individuals were compared before and after 2000, and 556 patients (34%) were in the intellectual disability range. After 2000, the most significant improvement in neuropsychological outcomes was in the NAGS deficiency cases, with the prevalence of intellectual disability decreasing from 50% to 9%, reflecting the effectiveness of *N*-carbamyl glutamate treatment, and the favorable results of some studies suggested that it is possible to prevent or reverse the negative impact of UCDs on neuropsychological functioning (5).

Table 2. Case progress and medication management

Date/Time	Clinical Status	Treatment Initiated / Modified	Dose	Clinical Response
Neonatal Period	Hyperammonemic metabolic decompensation	Protein-restricted diet initiated	-	Clinical stabilization following dietary intervention
Age 11	Diagnosis of NAGS deficiency and epilepsy	Carglumic Acid & Clobazam	3600 mg/ day & 30 mg/day	Initial treatment for metabolic disorder and seizures
Last 2 Years	Increased aggressive behaviors	Not specified	-	Persistent behavioral issue
2023	Suicide attempt	Aripiprazole	5 mg/day	Persistent mood lability
1 Week Later	Mood lability	Aripiprazole (dose increase)	10 mg/day	Continued clinical managemen
Simultaneous	Behavioral symptoms	Haloperidol	0.5 mg/day	Adjunctive treatment
Pediatric Neurology Consultation	VA contraindicated (hyperammonemia risk)	Lamotrigine	25 mg/day	Triggered DRESS Syndrome.
Day 17 (Lamotrigine)	Skin discoloration, fever, dilated pupils, somnolence	Hospitalization / drug discontinuation	-	Diagnosis: DRESS syndrome (admitted to immunology).
Current Status	Post-recovery from DRESS	Aripiprazole (dose adjusted)	15 mg/day	Mood disorder symptoms are under control

A case with NAGS deficiency with psychotic features, which is also rarely reported in the literature, was presented in another study (11). Likewise, in the literature, a female patient who presented with recurrent vomiting attacks, psychotic behaviors, and confusion during adolescence until she was diagnosed with partial NAGS deficiency at the age of 13 was reported (14). In the report of an

adolescent male patient with chronic psychological symptoms starting in late childhood, it was stated that when he was about 9 years old, his conduct started to change, with attention deficit and learning disabilities, episodes of anxiety and irritability, and hand tremors. At 12 years of age, he was admitted to the hospital because of an episode of acute headache, vomiting, and confusion, without fever, and NAGS deficiency was diagnosed in the patient (11).

In a study evaluating a total of 229 UCD patients, it was reported that 35% of the patients had abnormal magnetic resonance imaging (MRI) or computed tomography findings, and 26% had abnormal brain waves (15). Our patient, who did not have seizures in the first years of her life, had a seizure at the age of 11 years and was diagnosed with epilepsy, and mood lability was added to her clinical records. The EEG performed in September 2024 and brain MRI performed in 2020 showed normal results.

In a review of cases with NAGS deficiency in 2020, it was reported that 18% of the cases had consanguinity between the parents (6). In our case, the parents were also related. NAGS deficiency is the only treatable UCD (16). The mainstay of treatment has been the reduction of ammonia through dietary restriction and/or alternative route therapies. This disease can currently be treated using carglumic acid, an N-acetyl glutamate analog, and a low-protein diet when starting treatment (16,17). Approved in 2010 by the FDA, carglumic acid is the treatment of choice for NAGS deficiency (16,18). However, there is insufficient data on the clinical response of these cases and the side effects of the selected drugs in the presence of comorbidities such as epilepsy and mood disorders. For example, a case who developed hyperammonemia due to VA use and was diagnosed with underlying NAGS deficiency was presented (19). In the aforementioned case, when VA treatment was stopped, and the treatment regimen was switched to lamotrigine, it was reported manic symptoms reappeared after the cessation of lamotrigine treatment. Then, VA treatment was restarted with weekly follow-ups after the third weekly visit, as manic symptoms worsened, and concerns about rashes were reported (19). In this case, VA was the only effective therapeutic option and was therefore initiated despite the presence of hyperammonemia. Subsequent diagnostic evaluation revealed a genetically confirmed NAGS deficiency. Following this diagnosis, carglumic acid therapy was started, and it resulted in significant clinical and biochemical improvement (19).

Neuropsychiatric/neurodevelopmental findings are common among the initial symptoms of late-onset UCDs, and serum ammonia levels should be checked in the presence of unexplained or treatment-resistant neuropsychiatric/neurodevelopmental symptoms that emerge during childhood or adolescence (20).

DRESS syndrome usually starts abruptly with maculopapular morbilliform exanthema with a fever of >38°C as of 2–3 weeks after the introduction of the implicated drug (21). It classically occurs 3 weeks–3 months after exposure to a limited number of drugs, mainly anticonvulsants, antibiotics, and sulfonamides (8,22,23). Indeed, the five drugs (carbamazepine, phenytoin, phenobarbital, zonisamide, and lamotrigine) mainly associated with DRESS have not changed significantly over the last 15 years (24). Common pharmacological triggers for pediatric DRESS syndrome include aromatic anticonvulsants, responsible for 50% of cases (mainly carbamazepine, phenytoin, and phenobarbital), antibiotics, responsible for up to 30% of cases (mainly vancomycin, trimethoprim-sulfamethoxazole, and amoxicillin) and, although infrequent, sulfasalazine (4.6%) and nonsteroidal anti-inflammatory drugs (4.6%) (25).

DRESS syndrome is an adverse drug reaction characterized by widespread skin involvement, fever, lymphadenopathy, visceral involvement, and laboratory abnormalities (e.g., eosinophilia, mononucleosis-like atypical lymphocytes) (24,25). A review of 16 case studies of pediatric patients with lamotrigine-induced drug-induced hypersensitivity syndrome (DIHS)/DRESS revealed that DRESS should be considered in patients exhibiting both a dermatological rash and impaired liver function

several weeks after initiating an anticonvulsant medication. It is more common in adults and only rarely seen in children, in whom it is frequently associated with systemic organ involvement, such as liver dysfunction, renal impairment, and interstitial pneumonitis. Myocarditis, thyroiditis, encephalitis, and type 1 diabetes mellitus have also been reported as manifestations of this syndrome (21).

Table 3. RegiSCAR score of our case

Score	-1	0	1	2	Our case
Fever ≥38.5°C	No/U	Yes			0
Enlarged lymph nodes		No/U	Yes		1
Eosinophilia		No/U			0
Eosinophils (×10⁹/L)			0.7–1.49	≥1.5	
Eosinophils if leukocytes <4×10⁹/L			10–19.9%	≥20%	
Atypical lymphocytes		No/U	Yes		0
Skin involvement					
Skin rash extent >50% BSA		No/U	Yes		1
Skin rash suggesting DRESS	Nu	U	Yes		1
Biopsy suggesting DRESS	No	Yes/U			0
Organ involvement					
Liver		No/U	Yes		1
Kidney		No/U	Yes		0
Lung		No/U	Yes		0
Muscle/heart		No/U	Yes		0
Pancreas		No/U	Yes		0
Other organ		No/U	Yes		0
Resolution ≥15 days		No/U	Yes		1
Evaluation of other potential causes					
ANA					
Blood culture					
Serology HAV/HBV/HCV					
Chlamydia/mycoplasma					
If none positive and ≥3 above negative			Yes		1
Total score					6

Additionally, the data suggest adult and pediatric DRESS cases are not significantly different in terms of their clinical manifestations (24). Nevertheless, pediatric DRESS syndrome should be considered when a child presents with fever, maculopapular eruption, lymphadenopathy, eosinophilia, and visceral involvement, and the onset of the symptoms may be delayed (2–6 weeks) or rapid (<15 days) (25). The review of the relevant literature and the experience of these cases suggest that the risk of lamotrigine-associated severe cutaneous adverse reactions is increased when starting lamotrigine treatment at high initial doses, and we recommend practitioners be alerted of the risk of severe cutaneous drug reactions particularly at initial doses greater than 25 mg (23). In our case, DRESS syndrome developed after lamotrigine use, and the patient was hospitalized in the pediatric inpatient clinic. Our patient also developed skin discoloration, fever and spotting, dilated pupils, and constant sleepiness on the 17th day of her lamotrigine treatment. The patient's RegiSCAR score is presented in Table 3 (26).

DRESS syndrome is an acute, severe, and life-threatening disease with a mortality rate of about 10%, but most patients with DRESS have a full recovery (21,23,24,27). Similarly, the early recognition of the

condition and the early withdrawal of allergenic drugs is a very important aspect of the management of DRESS (21). Glucocorticoid therapy is the first-choice treatment, and plasma exchange, intravenous immunoglobulin (IVIG), and immunosuppressant drugs should be considered in cases with multiorgan involvement and life-threatening complications (21). In these cases, like in our case, clinical recovery occurs as a result of ceasing treatment with the implicated drug and providing steroid treatment (8).

CONCLUSION

Patients with NAGS deficiency, as in our case, are prone to serious drug side effects and neuropsychiatric disorders that need to be closely monitored. The timely diagnosis of these patients is important, and treatment should be started immediately to prevent complications. This case highlights lamotrigine-induced DRESS syndrome in a patient with NAGS deficiency, epilepsy, and mood disorder, demonstrating that individuals with underlying metabolic disorders may be more vulnerable to severe idiosyncratic drug reactions. The early recognition of DRESS and prompt discontinuation of the suspected or causative agent are critical to prevent life-threatening complications in this vulnerable population.

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The authors declare that they have no conflict of interests regarding content of this article.

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Ethical Declaration

Informed consent was obtained from the participant and Helsinki Declaration rules were followed to conduct this study.

Authorship Contributions

Concept: SS, PCR, Design: SS, PCR, AYT, DK, Supervising: PCR, GG, AYT, DK, Financing and equipment: SS, PCR,, Data collection and entry: SS, PCR, AYT, GG, DK, Analysis and interpretation: SS, PCR, GG, Literature search: SS, PCR, DK, Writing: SS, PCR, DK, Critical review: PCR, AYT, GG.

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Scientific Reports in Medicine

Case Report

Pembrolizumab-associated acute tubular interstitial nephritis with asymptomatic serum creatinine elevation: A case report

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Abstract

Immune checkpoint inhibitors (ICPIs) have transformed cancer treatment but may cause immune-related adverse events (irAEs) affecting multiple organ systems. Renal irAEs, particularly tubulointerstitial nephritis (TIN), are uncommon yet clinically significant, and their optimal diagnosis and management — including the decision to rechallenge — remain areas of active investigation.

A 59-year-old male with metastatic lung adenocarcinoma and high PD-L1 expression (TPS 80%) received pembrolizumab monotherapy. After eight cycles, asymptomatic acute kidney injury (AKI; serum creatinine 2.97 mg/dL) was detected during routine monitoring. Clinical and laboratory evaluation — including peripheral eosinophilia and pyuria with leukocyte casts on urine microscopy — supported a diagnosis of TIN without recourse to kidney biopsy. The Naranjo Adverse Drug Reaction Probability Scale score was 8, indicating a probable association with pembrolizumab. Prednisolone was initiated, and serum creatinine returned to baseline within 5 days. Following complete renal recovery and a joint oncology–nephrology risk–benefit assessment, pembrolizumab was successfully rechallenged. The patient completed 12 additional cycles with stable renal function and no recurrence of AKI.

This case demonstrates that pembrolizumab-associated TIN may present as entirely asymptomatic creatinine elevation, underscoring the importance of routine biochemical monitoring. A biopsy-free diagnostic approach was feasible when clinical and laboratory findings were concordant. The successful rechallenge outcome contributes to the limited evidence supporting individualized ICPI resumption following grade 3 renal irAEs.

Keywords: Pembrolizumab, Immune-related adverse events, Acute tubulointerstitial nephritis, Acute kidney injury, Rechallenge, Lung adenocarcinoma

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INTRODUCTION

The immune checkpoint inhibitors (ICPIs) are monoclonal antibodies that target inhibitory receptors on T cells, other immune cells, and tumor cells (1, 2). However, treatment-related primary and acquired resistance and side effects are crucial problems (3–5). The most important side effects of immunotherapy treatment are immune-related adverse events (irAEs), which are autoimmune conditions that can be seen in all organs. Renal side effects are relatively less frequent, although gastrointestinal, skin, and endocrine irAEs are more common (5). Awareness, early diagnosis, and treatment are essential for toxicities that can be seen in almost all organs at any stage of treatment. We report a case of tubulointerstitial nephritis associated with immunotherapy (pembrolizumab) diagnosed and treated without renal biopsy.

CASE REPORT

A 59-year-old male patient presented to Cukurova University Faculty of Medicine, Department of Medical Oncology, without any documented comorbidities. He experienced right upper quadrant pain in July 2023. A thorax tomography showed a 62×54 mm consolidation area that was continuous with the bronchus in the upper part of the right lower lobe. The biopsy revealed that the condition was lung adenocarcinoma. PET/CT showed bone metastases, a lesion in the left adrenal gland, lymphadenopathy in the right lower paratracheal, subcarinal/subcarinal right paraesophageal, and right hilar regions. No driver mutation was identified. The PD-L1 Tumor Proportion Score (TPS) was 80%. The patient commenced treatment with pembrolizumab 200 mg on July 7, 2023, every 3 weeks (q3w). Baseline laboratory findings at the time of immunotherapy initiation are summarized in **Table 1**; all parameters were within normal reference ranges. Hypothyroidism was diagnosed 3 months after pembrolizumab treatment was initiated (October 2023, TSH: 96 mIU/L). Levothyroxine 100 mcg was started. Pembrolizumab treatment was continued under levothyroxine treatment. TSH level became normalized.

Table 1. Baseline Laboratory Findings at Immunotherapy Initiation (July 2023)

Parameter	Value	Reference Range
Biochemistry		
Serum creatinine	0.90 mg/dL	0.70–1.20 mg/dL
Blood urea nitrogen (BUN)	16 mg/dL	6–20 mg/dL
Aspartate aminotransferase (AST)	24 U/L	0–40 U/L
Alanine aminotransferase (ALT)	28 U/L	0–41 U/L
Albumin	4.1 g/dL	3.5–5.2 g/dL
Thyroid stimulating hormone (TSH)	1.45 mIU/L	0.4–4.0 mIU/L
Hematology		
Hemoglobin	13.4 g/dL	13.0–17.5 g/dL
White blood cell count (WBC)	$6.80 \times 10^3/\mu L$	$4.00–10.00 \times 10^3/\mu L$
Neutrophils	$4.10 \times 10^3/\mu L$	$2.00–7.00 \times 10^3/\mu L$
Eosinophils	$0.12 \times 10^3/\mu L$	$0.00–0.50 \times 10^3/\mu L$
Platelets	$265 \times 10^3/\mu L$	$150–450 \times 10^3/\mu L$
Urinalysis		
Protein	Negative	Negative
Leukocyte esterase	Negative	Negative
Erythrocytes	0–1 /HPF	0–3 /HPF
Leukocytes	0–1 /HPF	0–5 /HPF

The patient, who had completed eight cycles of treatment, presented for the ninth cycle on February 22, 2024, for routine examinations. Despite the patient's lack of complaints, we detected acute renal failure (serum creatinine 2.97 mg/dL, Figure 1). Postrenal obstruction was excluded with USG. At the time of AKI detection, the patient's only concomitant medication was levothyroxine for pembrolizumab-associated hypothyroidism. Notably, no medications commonly implicated in drug-induced acute interstitial nephritis — including proton pump inhibitors, nonsteroidal anti-inflammatory drugs, and antibiotics — were being administered. The complete blood count revealed the presence of eosinophilia (Figure 2). The 24-hour urine protein excretion was 647 mg/day. Urine microscopy demonstrated pyuria with leukocyte casts, findings suggestive of acute interstitial nephritis (Figure 3).

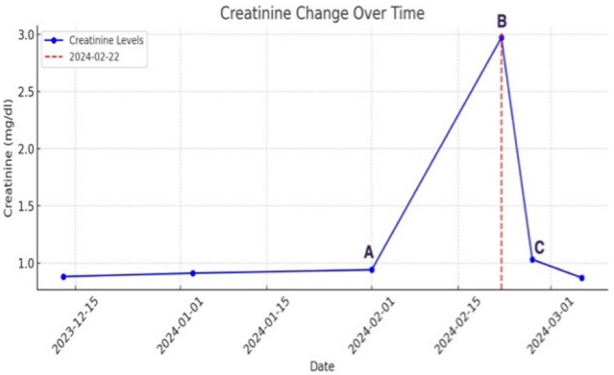

Figure 1. Serial serum creatinine levels during pembrolizumab treatment, showing the rise at the time of acute kidney injury detection and subsequent recovery following corticosteroid therapy.

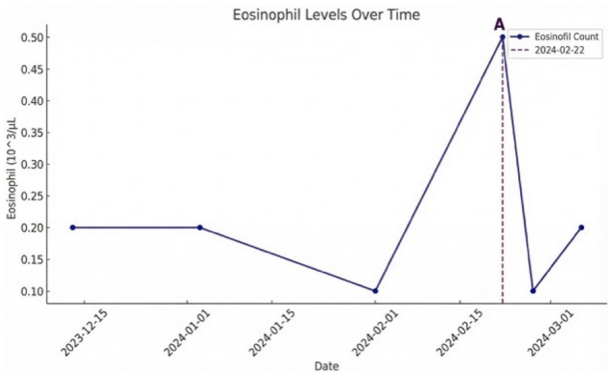

Figure 2. Eosinophil kinetics during the course of treatment. **(A)** Peak eosinophil count concurrent with acute kidney injury onset. **(B)** Trend of absolute eosinophil count over time, demonstrating normalization following pembrolizumab discontinuation and corticosteroid initiation.

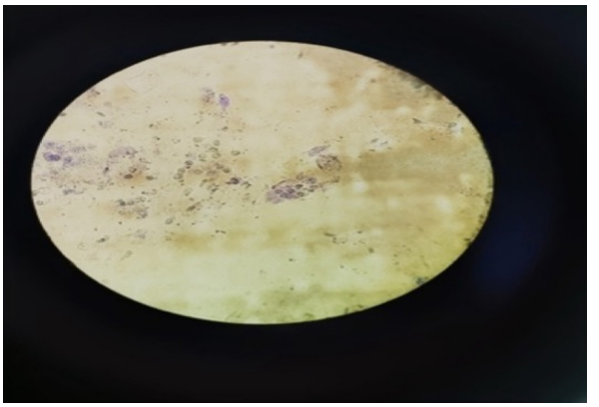

Figure 3. Urine microscopy demonstrating pyuria with leukocyte casts, findings supportive of acute interstitial nephritis.

The pembrolizumab treatment for the patient was discontinued. We initiated prednisolone at a dose of 32 mg/day (approximately 0.5 mg/kg based on the patient's body weight of 65 kg). Although this dose was lower than the 1 mg/kg/day recommended by current guidelines, the decision was based on clinical judgment given the patient's asymptomatic presentation and hemodynamically stable condition. Serum creatinine declined from 2.97 mg/dL to 1.03 mg/dL within approximately 5 days, indicating a prompt and complete response. A week later, we determined the creatinine levels to be 0.91 mg/dL. Following the treatment with prednisolone, eosinophil counts returned to normal range. The daily dose of prednisolone was reduced to 16 mg after two weeks and to 8 mg after one week, and subsequently discontinued.

Following complete renal recovery and discontinuation of prednisolone, the patient resumed his ninth cycle of pembrolizumab treatment on March 19, 2024, at a dosage of 200 mg q3w. The rechallenge decision was made jointly by the treating oncologist and a consulting nephrologist after careful risk–benefit assessment. Serum creatinine was monitored before each subsequent cycle. As of December 2024, the patient has received 12 additional cycles with stable renal function and no recurrence of AKI.

DISCUSSION

Immunotherapies have entered clinical use in many solid and hematologic tumors, particularly melanoma, lung cancer, and kidney cancer. irAEs are frequently observed between weeks 2 and 16 depending on the organ in which they develop. However, it should be kept in mind that they may occur at any period of treatment or even up to 1 year after treatment is discontinued. Compared to monotherapy, there is a higher incidence of irAEs with combination therapy. In our case, acute renal failure was detected about 7 months after starting pembrolizumab. Interestingly, the patient had no complaints and it was detected during routine follow-up visits.

Renal side effects associated with immunotherapy are less common and there are some problems with the definition of acute kidney injury (AKI). Kidney Disease: Improving Global Outcomes Working Group (KDIGO) consensus criteria define acute kidney failure based on relative changes in serum creatinine levels. For example, an increase of up to 1.5 times the upper limit of normal for creatinine increase is defined as grade 1. However, muscle wasting may occur in cancer patients and significant increases in serum creatinine levels may be considered "normal". In addition, conditions requiring hospitalization for AKI are defined as grade 3, while there are no defined criteria for grades 1 and 2 (6–11).

The prevalence of immune checkpoint inhibitor–associated acute kidney injury (ICPIs-AKI) is predicted to be between 1.4% and 4.9%. Tubulointerstitial nephritis (TIN) was initially identified as the predominant renal lesion caused by immune checkpoint inhibitor (ICPI) therapy. However, other immune-mediated diseases, such as different types of glomerulonephritis, have also been documented (12). Acute kidney injury (AKI) occurred at a median of 14 weeks (interquartile range [IQR], 6–37) following the commencement of immune checkpoint inhibitor (ICPi) treatment, and 2 weeks (IQR, 2–3) after the last dose of ICPi. The severity of AKI was classified as stage 2 in 43% of patients, stage 3 in 57% of patients, and 9% of patients required renal replacement therapy (RRT). In 43% of instances, an extrarenal immune-related adverse event (irAE), typically a rash, occurred either before or at the same time as acute kidney injury (AKI) (12). The occurrence of pembrolizumab-related tubulointerstitial nephritis (TIN) in our case was similarly in line with the existing literature. AKI in cancer patients can be caused by dehydration, infection, adverse drug reaction, contrast and analgesic nephropathy, tumor lysis syndrome, or postrenal obstruction. Acute interstitial nephritis (AIN) is the most common pathology. Other pathologies include glomerular diseases such as minimal change disease, acute tubular necrosis (ATN), and thrombotic microangiopathy. ICPIs rarely lead to the development of glomerular disease. Patients who develop minimal change disease, focal segmental glomerulosclerosis, or membranous nephropathy often present with nephrotic syndrome (13–17). The Naranjo Adverse Drug Reaction Probability Scale score in our case was 8, indicating a probable adverse drug reaction (18). Detailed item-by-item scoring with explicit justification is provided in **Supplementary Table 1**. The patient's concurrent hypothyroidism also provides evidence for pembrolizumab-associated TIN.

The gold standard for the diagnosis of ICPI-related glomerular diseases and AKI is a kidney biopsy. However, a kidney biopsy may not always be necessary. All causes of AKI should be ruled out in the differential diagnosis (5). In our case, there was no evidence of dehydration among the possible causes of AKI, postrenal causes were excluded by abdominal USG, and the patient was not receiving any concomitant nephrotoxic medications or drugs commonly associated with acute interstitial nephritis, such as proton pump inhibitors, nonsteroidal anti-inflammatory drugs, or antibiotics. Platelet count and coagulation parameters were within normal limits; thus, the decision to forgo kidney biopsy was not attributable to procedural contraindications. Rather, the combination of temporal association with

pembrolizumab, peripheral eosinophilia, pyuria with leukocyte casts on urine microscopy, the systematic exclusion of alternative etiologies, and the concurrent presence of another irAE (hypothyroidism) provided sufficient diagnostic confidence for pembrolizumab-associated tubulointerstitial nephritis without histological confirmation.

Guidelines recommend discontinuation of treatment in case of grade 2 or higher toxicity.

Supplementary Table 1. Adverse Drug Reaction Probability Scale (Naranjo Algorithm Assessment)

Scoring interpretation: ≤0 = Doubtful; 1–4 = Possible; 5–8 = Probable; ≥9 = Definite

No.	Question	Yes	No	Do not know	Score	Justification
1	Are there previous conclusive reports on this reaction?	+1	0	0	+1	Pembrolizumab-associated TIN has been reported in multiple published studies (Cortazar et al., 2020; Gupta et al., 2020).
2	Did the adverse event appear after the suspected drug was administered?	+2	−1	0	+2	AKI was detected after 8 cycles of pembrolizumab (approximately 7 months after initiation).
3	Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	+1	Serum creatinine improved from 2.97 to 1.03 mg/dL within 5 days of pembrolizumab discontinuation and corticosteroid initiation.
4	Did the adverse reaction reappear when the drug was readministered?	+2	−1	0	0	AKI did not recur during 12 additional cycles of rechallenge; scored as "Do not know" to reflect uncertainty regarding influence of monitoring protocol.
5	Are there alternative causes (other than the drug) that could on their own have caused the reaction?	−1	+2	0	+2	Dehydration, infection, nephrotoxic drugs, contrast nephropathy, and postrenal obstruction were systematically excluded.
6	Did the reaction reappear when a placebo was given?	−1	+1	0	0	No placebo was administered.
7	Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	0	Pembrolizumab serum levels were not measured; therapeutic drug monitoring is not standard practice for ICPIs.
8	Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0	0	Dose was not modified; pembrolizumab was administered at the standard flat dose of 200 mg throughout.
9	Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	+1	The patient developed pembrolizumab-associated hypothyroidism (another irAE) 3 months after treatment initiation.
10	Was the adverse event confirmed by any objective evidence?	+1	0	0	+1	Elevated serum creatinine (2.97 mg/dL), peripheral eosinophilia, pyuria with leukocyte casts, and proteinuria.
					Total = 8	**Probable adverse drug reaction**

Corticosteroids are recommended as initial treatment, although the specific dosage may differ between treatment guidelines. However, when toxicity decreases to grade 1, nearly all guidelines recommend a progressive reduction in corticosteroid dosage. Approximately 85% of patients with AKI respond to corticosteroids with partial or complete improvement. Patients who fail to recover within

one week should be closely monitored, and alternative immunosuppressive agents such as cyclophosphamide, azathioprine, cyclosporine, infliximab, or mycophenolate mofetil should be contemplated (4). In our case, AKI improved on the 5th day of corticosteroid treatment despite an initial prednisolone dose (0.5 mg/kg/day) that was lower than the guideline-recommended 1 mg/kg/day. The rapid and complete renal recovery observed with this lower dose may suggest that not all patients with grade 3 ICPI-associated AKI require full-dose corticosteroid therapy, although this observation from a single case warrants further investigation.

Patients who develop AKI in conjunction with irAEs also have their treatment interrupted, and in certain cases, it is entirely discontinued. The ASCO guideline advises permanent discontinuation of ICPIs in patients who experience grade 3 or higher renal toxicity (3). Nevertheless, this recommendation must be weighed against individual clinical circumstances, particularly when limited therapeutic alternatives exist. In the present case, the decision to rechallenge with pembrolizumab was made jointly by the treating oncologist and a consulting nephrologist following a comprehensive risk–benefit assessment. Several patient-specific factors supported this decision: first, complete recovery of renal function to baseline values (serum creatinine 0.91 mg/dL) following corticosteroid therapy; second, the achievement of stable disease under pembrolizumab, indicating ongoing clinical benefit; third, the absence of actionable driver mutations and high PD-L1 expression (TPS 80%), which rendered pembrolizumab monotherapy the most appropriate and practically the only viable systemic treatment option; and fourth, the successful completion of the full corticosteroid taper prior to rechallenge, suggesting resolution of the immune-mediated process. To mitigate the risk of recurrent nephrotoxicity, serum creatinine was monitored before each subsequent pembrolizumab cycle. Reassuringly, the patient completed 12 additional cycles without recurrence of AKI, with stable renal function maintained throughout. Although AKI recurrence has been reported in 8–40% of patients who undergo ICPI rechallenge (10, 19), our experience adds to the growing evidence that carefully selected patients with complete renal recovery may safely resume ICPI therapy under close monitoring.

CONCLUSION

This case illustrates that pembrolizumab-associated tubulointerstitial nephritis may present with entirely asymptomatic serum creatinine elevation, reinforcing the necessity of routine biochemical monitoring at each treatment cycle. The combination of peripheral eosinophilia, pyuria with leukocyte casts, and the exclusion of alternative etiologies enabled a confident clinical diagnosis without recourse to kidney biopsy, allowing prompt initiation of corticosteroid therapy. Furthermore, the successful rechallenge with pembrolizumab — undertaken through a joint oncology–nephrology decision following complete renal recovery — demonstrates that carefully selected patients may safely resume ICPI therapy under close surveillance. These findings contribute to the limited but growing evidence base guiding the management of ICPI-associated renal toxicity in clinical practice.

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Informed consent was obtained from the participant and Helsinki Declaration rules were followed to conduct this study.

Authorship Contributions

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Scientific Reports in Medicine

Review

Global Warming and Allergy

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Abstract

Climate change, triggered by anthropogenic carbon dioxide emissions, may lead to increased morbidity and mortality in allergic diseases due to factors such as elevated and novel pollen production, storms, high temperatures, migration with exposure to air pollution, increased humidity, indoor mold and fungal proliferation, ozone elevation, biodiversity loss, and alterations in the microbiota. Strategies should be developed to reduce greenhouse gases and chemical and biological air pollutants, to inform the public accurately, and to implement preventive and therapeutic measures during high-allergen seasons.

Keywords: Allergic diseases, Global warming, Climate change, Asthma, Allergic rhinitis, Allergic conjunctivitis, Atopic dermatitis

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INTRODUCTION

Global warming is one of the most significant challenges of the twenty-first century. It refers to an increase in the average atmospheric temperature of the Earth caused by elevated levels of methane, carbon dioxide, chlorofluorocarbons, and various other pollutants, resulting in the greenhouse effect (1,2). Global warming is expected to cause numerous direct and indirect health problems in humans, one of which is an increase in allergic conditions. Genetic predisposition as well as environmental triggers such as foods, dust mites, pollens, molds, and animal dander may precipitate allergic diseases. Climate change influences both the levels and geographic distribution of aerosolized allergens (3). Allergic diseases affect approximately 20% of the global population (5). Climate change, in conjunction with increased air pollution and urbanization, contributes to the rising prevalence of allergic diseases (4). The increased prevalence cannot be explained solely by genetic factors (6). The phenotypes of allergic conditions such as atopic eczema, food allergy, asthma, allergic rhinitis, and allergic conjunctivitis can be significantly influenced by environmental factors (5,6). Global warming directly impacts the increase in allergic diseases through elevated particulate matter (PM) and pollen counts, and indirectly through droughts, floods, water pollution, migration, and heat waves, negatively affecting all allergic diseases from the prenatal period to death (7). Rising temperatures can directly or indirectly affect epithelial barriers of the skin and respiratory tract. Water pollution resulting from global warming and urbanization may also impair epithelial integrity, thereby exacerbating allergies (8). Climate change and global warming increase cadmium and zinc contamination in groundwater through leaching of heavy metals (9). Exposure to these potentially harmful metals has been reported to affect the T-cell population in umbilical cord blood, thereby contributing to the development of allergic diseases (10). Additionally, climate change reduces microbial diversity in the soil; coupled with increased hygiene, more time spent indoors, and reduced exposure to green spaces, farm animals, and pets, this has adverse effects on immune health. Reduced gut microbiota diversity has been linked to allergic, inflammatory, and autoimmune diseases. The gut microbiota plays a key role in the development of food allergies (10). Climate change, by increasing migration, urbanization, air pollution, and pollen exposure, also elevates the risk of developing respiratory conditions such as asthma (11).

Asthma and Allergic Rhinitis

The Sixth Assessment Report of the Intergovernmental Panel on Climate Change (IPCC) in 2022 emphasized that respiratory diseases, particularly asthma, are climate-sensitive (12). The airway from the larynx to the alveolar wall is predominantly innervated by vagal nerves containing transient receptor potential (TRP) channels. TRPV1 and TRPV4 receptors are sensitive to temperatures above 42°C and between 22–40°C, respectively. These receptors are activated when hot air is inhaled (13,14). High temperatures and heat waves directly increase asthma exacerbations and hospital admissions (15–17). Climate change-induced heavy rains and flooding promote indoor humidity and mold growth in affected households, negatively impacting indoor air quality (18). Thunderstorm asthma refers to a surge in asthma cases following thunderstorms during periods of high pollen counts. In 2016, a thunderstorm asthma outbreak occurred in Melbourne, Australia. The combination of storm, wind, and high humidity caused ryegrass pollen grains to swell and rupture under strong winds, releasing microscopic particles capable of reaching deeper airways. Rapid meteorological changes—such as a sudden 10°C temperature drop and humidity levels exceeding 70% within an hour—exacerbated the event's severity. This outbreak resulted in 10 deaths and 9,000 emergency department presentations. Patients with allergic rhinitis but without a prior asthma diagnosis were at significant risk. Increased humidity also leads to proliferation of mold spores, raising indoor aeroallergen exposure and worsening respiratory

allergic symptoms. Populations with asthma and allergic rhinitis are particularly vulnerable to global warming (19–21). Ozone, a major greenhouse gas and potent oxidant, is associated with airway irritation, inflammation, oxidative stress, reduced lung function, and increased epithelial barrier permeability. In addition to pollen, weather, and air quality, ozone can influence the severity of pollen allergy symptoms. Globally, 8–20% of asthma-related emergency visits are attributed to ozone exposure (22).

Allergic Conjunctivitis

Global warming also plays a role in allergic conjunctivitis exacerbations. Climate change increases the availability rather than the structural changes of pollen grains and fungal spores (23,24). Evidence suggests that rising temperatures and elevated carbon monoxide levels have direct effects on plants and pollen production (25). Elevated carbon dioxide levels are thought to increase pollen production in plants (26). Menzel's study, covering the period 1951–1996 in Europe, found that flowering and pollen production periods started earlier and lasted longer over time (27). Pollen is one of the most prominent triggers of allergic conjunctivitis, exerting effects via direct histamine release. Increases are expected with global warming.

Atopic Dermatitis

Increased temperatures due to global warming lead to more sweating, and the salts and other substances in sweat aggravate itching and inflammation in already sensitive skin. As atopic dermatitis worsens, higher glucose levels in sweat may delay wound healing (28). During extreme weather events such as Hurricane Katrina in the USA in 2005, flooding led to increased mold proliferation both indoors and outdoors (29). Individuals with atopic dermatitis may develop allergic reactions to molds and perceive them as high threats, leading to exacerbated skin irritation (30). These factors collectively intensify itching, irritation, and inflammation in atopic skin.

Food Allergy

Climate change may alter the geographic distribution and growing conditions of food crops, leading to population exposure to new plant-derived foods and potentially reshaping regional patterns of food allergy (31). Shifts in cultivation areas may introduce allergenic proteins to previously unexposed populations, increasing the risk of sensitization.

Elevated atmospheric carbon dioxide levels have also been shown to influence plant physiology and allergen expression. Studies in peanut cultivars demonstrate changes in biomass and allergenicity under increased carbon dioxide conditions, suggesting that atmospheric changes can modify both the quantity and immunogenic properties of allergenic proteins (31). Within the One Health framework, climate-related environmental stressors may further affect plant defense mechanisms and allergen production, potentially influencing food allergy patterns at the population level (32).

CONCLUSION

Global warming and climate change have significant effects on allergic and atopic diseases. Continuous monitoring of these climate-related changes, surveillance of particulate matter and pollutants, creation of pollen maps, development of emergency weather alert systems, and public awareness campaigns to prevent greenhouse gas emissions are essential. The anticipated increase in extreme weather events in the near future will likely result in new allergic attacks, diagnoses, and disease exacerbations. A comprehensive One Health approach should be adopted to address these challenges (32).

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Authorship Contributions

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