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Real-world efficacy of ramucirumab plus paclitaxel with or without nivolumab in patients with advanced gastric and gastroesophageal junction cancers

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MAIN POINTS

- Ramucirumab plus paclitaxel demonstrates consistent efficacy as a second-line treatment for advanced gastric/GEJ cancers in real-world settings.
- Although response rates were numerically higher with the addition of nivolumab to this combination, no statistically significant clinical benefit was observed.
- Ramucirumab plus paclitaxel (±ICI) may serve as an effective third-line treatment option in patients with good performance status.

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ABSTRACT

Aim: This study primarily aimed to assess the efficacy of second-line ramucirumab (RAM) plus paclitaxel (PTX) in patients with advanced gastric and gastroesophageal junction (GEJ) cancers and to compare its outcomes with those of RAM+PTX plus immune checkpoint inhibitor (ICI) in real-world practice. The secondary objective was to assess the safety of RAM+PTX (±ICI) and to explore its efficacy in later-line settings.

Materials and Methods: This single-center study retrospectively analyzed the clinicopathologic data of patients with advanced gastric/GEJ cancer treated with RAM+PTX, with or without an ICI, in second-line or later settings between January 2018 and September 2024. Efficacy was evaluated based on the objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), and overall survival (OS). We analyzed efficacy outcomes by treatment line.

Results: We identified 46 patients (female, 54.3%) who received RAM+PTX (±ICI). In the second-line setting, 27 patients (58.7%) received RAM+PTX, and 10 patients (21.7%) received RAM+PTX plus nivolumab. The ORRs were 18.5% and 30.0% (p=0.66), and the DCRs were 55.6% and 80% (p=0.26), respectively. The addition of nivolumab did not significantly improve survival outcomes (median PFS, 4.3 vs. 3.1 months; HR, 0.93; 95% CI, 0.44-1.98; p=0.85; median OS, 7.8 vs. 9.6 months; HR, 0.82; 95% CI, 0.35-1.91; p=0.64). Age ≥50 years (HR, 2.90; 95% CI, 1.24-6.78; p=0.014) and the presence of ascites (HR, 2.86; 95% CI, 1.14-7.16; p=0.025) were independently associated with poorer OS.

Conclusion: The real-world efficacy of RAM+PTX as second-line therapy in advanced gastric/GEJ cancers is consistent with the results of randomized trials, though grade ≥3 adverse events were more frequent. While adding nivolumab did not confer a statistically significant benefit, a numerical improvement in ORR and DCR indicates potential value that warrants further prospective evaluation.

Keywords: Immunotherapy, Stomach neoplasms, VEGFR-2, Ramucirumab

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INTRODUCTION

Globally, gastric and gastroesophageal junction (GEJ) cancers are the fifth most common cause of cancer-related death [1]. Current first-line systemic therapy for advanced gastric/GEJ cancers consists of platinum- and fluoropyrimidine-based chemotherapy, with the addition of human epidermal growth factor receptor 2 (HER2)-targeted agents and/or immune checkpoint inhibitors (ICIs) for selected patients [2]. Following failure of first-line therapy, subsequent systemic therapies demonstrate limited efficacy, and only 14–27% of patients are able to receive third-line systemic therapy in real-world practice [3,4]. The development of more effective second-line therapeutic options and combination strategies is essential to improve oncologic outcomes in advanced gastric/GEJ cancers.

Ramucirumab (RAM) is a fully human IgG1 monoclonal antibody that specifically binds to and blocks vascular endothelial growth factor receptor-2 (VEGFR-2) [5]. In the pivotal phase III RAINBOW trial, second-line treatment with RAM plus paclitaxel (PTX) improved overall survival (OS)

compared with PTX monotherapy, and this combination has become one of the recommended second-line treatment options for advanced gastric/GEJ cancers [2,6]. The efficacy and safety of incorporating immune checkpoint inhibitors (ICIs) into this regimen remain unclear and have been investigated only in small early-phase studies [7,8]. Despite the encouraging results of early-phase studies combining ICIs with RAM+PTX, evidence regarding their efficacy in the second-line treatment of advanced gastric/GEJ cancer remains limited. We conducted a retrospective study to explore the potential benefit of adding ICI to RAM+PTX. The primary objective of this study was to evaluate the efficacy of second-line RAM+PTX and to compare its outcomes with those of RAM+PTX combined with an ICI in real-world clinical practice. The secondary objective was to assess the safety profile of this regimen and to explore the efficacy of RAM+PTX in later-line settings.

MATERIALS AND METHODS

In this single-center study, we retrospectively analyzed the clinical and pathological data of patients with metastatic gastric/GEJ adenocarcinoma treated with RAM+PTX, with or without an ICI, in second-line or later settings between January 2018 and September 2024. Adult patients aged ≥18 years with metastatic gastric/GEJ adenocarcinoma who had experienced disease progression during first-line therapy were included. Patients who received RAM+PTX (±ICI) in later lines were also included. ICI was added to RAM+PTX at the discretion of the treating physicians, particularly for patients with programmed cell death ligand-1 combined positive score (PD-L1 CPS) ≥ 1, based on the results of early-phase studies [7,8]. As RAM and nivolumab are not reimbursed for second-line or later treatment of metastatic gastric/GEJ adenocarcinoma in Türkiye, only a limited number of patients are able to access RAM+PTX (±ICI). All eligible patients receiving these regimens in the second-line or later settings were included in the study. Patients were administered RAM at 8 mg/kg on days 1 and 15, PTX at 80 mg/m^2 on days 1, 8, and 15, and nivolumab at 3 mg/kg on days 1 and 15 of each 4-week cycle, continuing until disease progression or unacceptable toxicity. Each 4-week interval was counted as one treatment cycle. Data collected from these patients included baseline characteristics, treatment details, tumor response, treatment-related adverse events (TRAEs), laboratory results, and survival status. Efficacy was determined using the objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), and OS. Tumor responses were evaluated by investigators following the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 [9]. ORR represented the proportion of patients achieving a complete response (CR) or partial response (PR), while DCR included those with CR, PR, or stable disease (SD) as their best overall outcome. PFS was measured from the initiation of RAM+PTX (±ICI) to the date of disease progression or death. OS was measured from the initiation of RAM+PTX (±ICI) to death or the date of last follow-up for surviving patients. For patients with unknown survival status, survival data were censored at the most recent date on which the patient was confirmed to be alive based on medical documentation. Safety was assessed through TRAE analysis. All TRAEs were categorized and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0) [10]. We analyzed efficacy outcomes by treatment line, whereas TRAEs were evaluated across the entire study cohort.

This study adhered to the principles of Good Clinical Practice and was approved by the local institutional review board (Koç University Ethics Committee, Approval ID: 2025.096.IRB2.044). The institutional review board exempted the study from the requirement to obtain individual informed consent given the retrospective design of the study.

Statistical analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences software version 25.0 (IBM SPSS Inc., Chicago, IL, USA). Continuous variables were reported as medians with interquartile ranges (IQR), whereas categorical variables were presented as frequencies with percentages. Chi-squared or Fisher's exact tests were applied to compare percentages, as appropriate, based on sample size and expected cell counts. The follow-up duration was determined by the reverse Kaplan–Meier method, and PFS and OS were assessed via Kaplan–Meier estimates. Cox proportional hazards regression was used for the univariate and multivariate analyses. Variables showing an association at $p<0.10$ in univariate analysis, as well as the treatment arm (the primary exposure variable), were entered into the multivariate model to adjust for potential confounders while minimizing the risk of overfitting. A two-sided p value <0.05 was statistically significant.

RESULTS

We identified 46 patients (female, 54.3%) with metastatic gastric/GEJ adenocarcinoma who received RAM+PTX (±ICI) as second-line or later therapy. In the second-line setting, 27 (58.7%) patients received RAM+PTX alone, and 10 (21.7%) patients received RAM+PTX combined with nivolumab. In the third-line setting (n=9, 19.6%), 7 (15.2%) patients received RAM+PTX alone, whereas 2 (4.3%) received the same regimen combined with nivolumab.

In the second-line setting, the median (IQR) age was 50 (44-59) years for patients treated with RAM+PTX alone and 49 (38-62) years for those treated with RAM+PTX plus nivolumab (p=0.62) (Table 1). The majority of patients had tumors with diffuse histology (66.7% in the RAM+PTX group vs. 80.0% in the RAM+PTX+nivolumab group; p=0.73) and HER2-negative disease (88.9% vs. 100.0%;

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Table 1. Patient characteristics in the second-line and third-line groups and comparison of these features among the second-line treatment arms.

Variables	2L			3L
	RAM+PTX (n = 27)	RAM+PTX+ICI (n = 10)	P value	All patients (n = 9)
Age, median (IQR)	50 (44-59)	49 (38-62)	0.62[a]	51 (46-58)
Female, n (%)	14 (51.9)	6 (60.0)	0.73[b]	5 (55.6)
ECOG PS, n (%)				
0-1	24 (88.9)	9 (90.0)	1.0[b]	9 (100.0)
≥2	3 (11.1)	1 (10.0)		0
Primary tumor location, n (%)				
Cardia	9 (33.3)	2 (20.0)		1 (11.1)
Corpus	11 (40.7)	4 (40.0)	0.63[c]	3 (33.3)
Antrum	7 (25.9)	4 (40.0)		4 (44.4)
Unknown	0	0		1 (11.1)
Histological subtype, n (%)				
Diffuse	18 (66.7)	8 (80.0)	0.73[c]	5 (55.6)
Intestinal	4 (14.8)	1 (10.0)		0
Unknown	5 (18.5)	1 (10.0)		4 (44.4)
HER2 status, n (%)				
Negative	24 (88.9)	10 (100.0)	0.55[b]	9 (100.0)
Positive	3 (11.1)	0		0
MMR status, n (%)				
pMMR	23 (85.2)	10 (100.0)	0.56[c]	8 (88.9)
dMMR	0	0		1 (11.1)
Unknown	4 (14.8)	0		0
PD-L1 status, n (%)				
CPS<1	19 (70.4)	5 (50.0)	0.059[c]	3 (33.3)
CPS≥1	4 (14.8)	5 (50.0)		5 (55.6)
Unknown	4 (14.8)	0		1 (11.1)
Time to metastasis, n (%)				
Synchronous	18 (66.7)	7 (70.0)	1.0[b]	9 (100.0)
Metachronous	9 (33.3)	3 (30.0)		0
Peritoneal metastases, n (%)				
Yes	14 (51.9)	9 (90.0)	0.097[c]	5 (55.6)
No	9 (33.3)	1 (10.0)		4 (44.4)
Unknown	4 (14.8)	0		0
Liver metastases, n (%)				
Yes	5 (18.5)	5 (50.0)	0.094[b]	3 (33.3)
No	22 (81.5)	5 (50.0)		6 (66.6)
Unknown	0	0		0

[a] Mann–Whitney U test, [b] Fisher's exact test, [c] Chi-square test. CPS, combined positive score; dMMR, deficient MMR; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; ICI, immune checkpoint inhibitor; IQR, interquartile range; MMR, mismatch repair; PD-L1, programmed cell death ligand-1; pMMR, proficient MMR; PTX, paclitaxel; RAM, ramucirumab.

Table 2. The best overall response.

	2L			3L
	RAM+PTX (n = 27)	RAM+PTX+ICI (n = 10)	P value	All patients (n = 9)
Best overall response, n (%)				
Complete response (CR)	0	0		1 (11.1)
Partial response (PR)	5 (18.5)	3 (30.0)		2 (22.2)
Stable disease (SD)	10 (37.0)	5 (50.0)		3 (33.3)
Progressive disease (PD)	12 (44.4)	2 (20.0)		3 (33.3)
Objective response rate, n (%)	5 (18.5)	3 (30.0)	0.66[a]	3 (33.3)
Disease control rate, n (%)	15 (55.6)	8 (80.0)	0.26[a]	6 (66.7)

[a] Fisher's exact test.

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Table 3. Univariate and multivariate analyses assessing factors influencing overall survival in patients treated with second-line ramucirumab plus paclitaxel, with or without an immune checkpoint inhibitor.

Variables	Median OS, months (95% CI)	Univariate Analysis HR (95% CI)	P value[a]	Multivariate Analysis HR (95% CI)	P value[a]
Gender					
Female	9.6 (3.8-15.4)	0.74 (0.35-1.57)	0.43		
Male	8.9 (4.7-13.1)				
Age					
<50 years	11.0 (8.6-13.4)	2.53 (1.11-5.76)	**0.027**	2.90 (1.24-6.78)	**0.014**
≥50 years	6.3 (4.5-8.1)				
ECOG PS					
0-1	9.0 (5.2-12.9)	2.88 (0.96-8.66)	**0.059**	2.71 (0.85-8.65)	0.091
≥2	4.4 (2.8-5.9)				
Peritoneal metastases					
Yes	8.9 (5.3-12.5)	1.24 (0.52-2.96)	0.63		
No	9.0 (5.2-12.9)				
Liver metastases					
Yes	7.8 (2.3-13.3)	1.62 (0.71-3.68)	0.25		
No	8.9 (5.7-12.0)				
Ascites					
Yes	6.3 (4.1-8.5)	2.81 (1.23-6.43)	**0.014**	2.86 (1.14-7.16)	**0.025**
No	11.0 (7.9-14.1)				
CEA, µg/L					
<ULN	9.6 (4.2-14.9)	0.65 (0.28-1.50)	0.31		
≥ULN	9.0 (4.7-13.4)				
CA 19-9, U/mL					
<ULN	9.6 (7.1-12.1)	1.13 (0.49-2.63)	0.77		
≥ULN	5.5 (2.9-8.1)				
Treatment arm					
RAM+PTX	7.8 (4.2-11.3)	0.82 (0.35-1.91)	0.64	1.51 (0.56-4.08)	0.42
RAM+PTX+ICI	9.6 (7.6-11.5)				
PIV					
<460.46	9.6 (3.1-16.1)	1.16 (0.55-2.43)	0.70		
≥460.46	7.8 (4.9-10.6)				
PNI					
<37.01	6.3 (5.2-7.4)	0.61 (0.29-1.29)	0.19		
≥37.01	11.0 (8.3-13.7)				

[a] Cox proportional hazards regression. CEA, carcinoembryonic antigen; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; ICI, immune checkpoint inhibitor; OS, overall survival; PIV, pan-immune inflammation value; PNI, prognostic nutritional index; PTX, paclitaxel; RAM, ramucirumab; ULN, upper limit of normal.

Table 4. Treatment-related adverse events during treatment with ramucirumab plus paclitaxel, with or without immune checkpoint inhibitor.

Adverse events	Any grade, n (%)	Grade ≥3, n (%)
Anemia	42 (91.3)	18 (39.1)
Neutropenia	24 (52.2)	15 (32.6)
Thrombocytopenia	24 (52.2)	6 (13.0)
AST/ALT increased	27 (58.7)	5 (10.9)
Infection	12 (26.1)	9 (19.6)
Nausea-diarrhea	3 (6.5)	2 (4.3)
Neuropathy	2 (4.3)	0
Thrombosis/bleeding	7 (15.2)	4 (8.7)
Perforation/Fistula	3 (6.5)	2 (4.3)
Others	6 (13.0)	4 (8.7)

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

p=0.55). Mismatch repair deficiency (dMMR) was not detected in any patient. PD-L1 CPS was <1 in most patients (70.4%) treated with RAM+PTX alone, whereas it was ≥1 in half of the patients (50.0%) treated with RAM+PTX plus nivolumab (p=0.059). The percentages of patients with synchronous metastases were 66.7% and 70.0%, respectively

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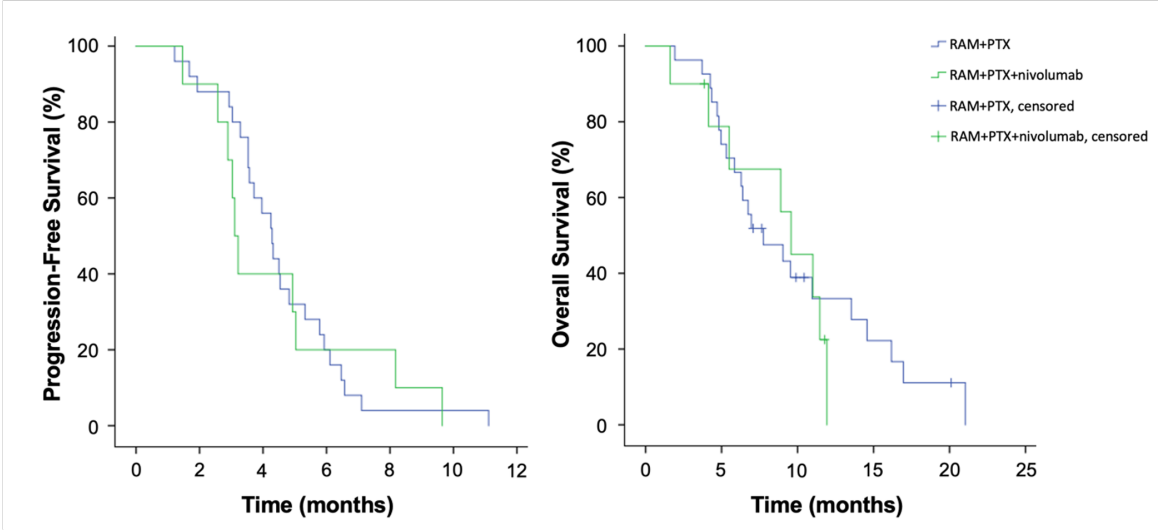

Figure 1. Progression-free survival and overall survival analyses of patients who received ramucirumab plus paclitaxel and those who received ramucirumab plus paclitaxel plus nivolumab as second-line treatment.

(p=1.0). Patients treated with RAM+PTX plus nivolumab showed higher frequencies of peritoneal (51.9% vs. 90.0%; p=0.12) and liver (18.5% vs. 50.0%; p=0.094) metastases, although not statistically significant. The median age in the third-line setting was 51 (46-58). Diffuse histology was observed in 55.6% of the patients, and all patients had HER2-negative disease. dMMR was observed in only one patient (11.1%), while 55.6% of patients had a PD-L1 CPS of ≥1. All patients had synchronous metastases, including peritoneal metastases in 55.6% and liver metastases in 33.3%.

In the second-line setting, the median follow-up duration was 20.1 months (95% confidence interval [CI], 8.1-32.1). The median (IQR) numbers of RAM and PTX cycles were both 4 (3-5) in RAM+PTX group. The median (IQR) numbers of cycles among those treated with RAM+PTX plus nivolumab were 5 (3-6) for RAM, 4 (3-6) for PTX, and 4 (3-6) for nivolumab. No significant differences in response rates or survival outcomes were observed between patients treated with RAM+PTX alone and those receiving RAM+PTX plus nivolumab. The ORRs were 18.5% and 30.0% in the RAM+PTX and RAM+PTX plus nivolumab groups, respectively (p=0.66) (Table 2). The DCRs were 55.6% and 80.0% in the RAM+PTX and RAM+PTX plus nivolumab groups, respectively (p=0.26). The median PFS was 4.3 months (95% CI 3.7-4.9) in the RAM+PTX group and 3.1 months (95% CI 2.8-3.4) in the RAM + PTX plus nivolumab group (hazard ratio [HR], 0.93; 95% CI, 0.44-1.98; p=0.85) (Figure 1). The median OS was 7.8 months (95% CI, 4.2-11.3) in the RAM+PTX group and 9.6 months (95% CI, 7.6-11.5) in the RAM+PTX plus nivolumab group (HR, 0.82; 95% CI, 0.35-1.91; p=0.64).

The median follow-up duration in the third-line setting was 10.0 months (95% CI, 0.0-36.5). The median (IQR) numbers of RAM and PTX cycles were 4 (3-7) and 4 (3-6), respectively. The ORR and DCR were 33.3% and 66.7%, respectively (Table 2). The median PFS was 6.6 months (95% CI, 0.0-17.1), and the median OS was 7.4 months (95% CI, 2.0-12.7).

In multivariate analyses of patients receiving second-line RAM+PTX (±ICI), age ≥50 years (HR, 2.90; 95% CI, 1.24-6.78; p=0.014) and the presence of ascites (HR, 2.86; 95% CI, 1.14-7.16; p=0.025) were independently associated with worse OS (Table 3).

The most common (>10%) grade 3 TRAEs while receiving RAM+PTX (±ICI) were anemia (39.1%), neutropenia (32.6%), infections (19.6%), thrombocytopenia (13.0%), and alanine aminotransferase and/or aspartate aminotransferase increase (10.9%) (Table 4). Seven patients (15.2%) experienced any-grade thrombosis and/or bleeding, while three patients (6.5%) experienced any-grade gastrointestinal perforation and/or fistula formation. Four patients (10.8%) receiving second-line treatment and two patients (22.2%) receiving third-line treatment discontinued therapy due to TRAEs.

DISCUSSION

Our results indicate that the real-world efficacy of RAM+PTX as second-line therapy for advanced gastric/GEJ cancers is consistent with the outcomes observed in randomized clinical trials. Nevertheless, grade ≥3 TRAEs were more common in our cohort. Our results also showed no clear benefit from adding an ICI to this regimen, despite numerically higher ORR and DCR in patients who received RAM+PTX plus ICI. Furthermore, our results indicate that RAM+PTX (±ICI) may serve as an effective third-line treatment option in patients with good performance status.

The therapeutic landscape of advanced gastric/GEJ cancers has been rapidly evolving in recent years with the incorporation of ICIs based on PD-L1 expression, microsatellite instability, and tumor mutational burden, as well as novel targeted agents directed against HER2, Claudin 18.2 (CLDN18.2),

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and fibroblast growth factor receptor 2 (FGFR2) [11]. However, available treatment options are still limited following progression on first-line platinum- and fluoropyrimidine-based chemotherapy with or without ICIs and/or targeted therapy, especially for patients ineligible for targeted agents or ICIs [2,11]. The phase III REGARD trial demonstrated that second-line RAM monotherapy significantly prolonged both PFS and OS compared with placebo (median PFS, 2.1 vs. 1.3 months; HR, 0.48; p<0.0001; median OS, 5.2 vs. 3.8 months; HR, 0.78; p=0.047), confirming the clinical relevance of VEGFR-2 inhibition in advanced gastric/GEJ cancer [12]. In the pivotal phase III RAINBOW trial, the combination of RAM+PTX significantly improved both PFS and OS compared with PTX monotherapy (median PFS, 4.4 vs. 2.9 months; HR, 0.64; p<0.0001; median OS, 9.6 vs. 7.4 months; HR, 0.81; p = 0.017), establishing this regimen as one of the recommended second-line treatments for advanced gastric/GEJ cancers [13]. In our cohort, while the median PFS was comparable to that observed in the RAINBOW trial, the ORR, DCR, and median OS were numerically lower, with the RAINBOW trial reporting ORR and DCR of 28% and 80%, respectively [13]. Differences in histological subtype distribution may partly explain these findings. In the RAINBOW trial, the clinical benefit of adding RAM to PTX was more pronounced in patients with intestinal-type histology [13]. Consistently, in a real-world analysis, Fountzilas et al. reported that the OS advantage of second-line RAM+PTX was confined to the intestinal subtype, with no significant benefit in diffuse or mixed histologies [14]. In our study, intestinal-type tumors represented only 14.8% of patients in the second-line RAM+PTX group, compared with 44% in the RAINBOW cohort [13].

Based on the results of the CheckMate-649 and KEYNOTE-859 trials, the addition of nivolumab for patients with PD-L1 CPS ≥ 5 or pembrolizumab for patients with PD-L1 CPS ≥ 10 to first-line platinum- and fluoropyrimidine-based combination chemotherapy has become the standard of care in advanced gastric/GEJ cancers [15,16]. However, the efficacy and safety of adding ICI to second-line RAM+PTX in patients who did not receive ICI in the first-line setting remain under investigation. A phase I/II trial reported encouraging efficacy with the combination of RAM+PTX and nivolumab, particularly among patients with PD-L1 CPS ≥1, representing 60.5% of the study population (n = 43) [7]. Patients with PD-L1 CPS ≥1 showed higher ORR (46.2% vs. 30.8%), longer median PFS (6.4 vs. 5.1 months), and longer median OS (13.8 vs. 8.0 months) than those with CPS <1. Notably, grade ≥3 TRAEs occurred in 90.7% of patients. Another phase II study investigating the efficacy and safety of avelumab with RAM+PTX as second-line treatment reported a 6-month OS rate of 71.2% and a median OS of 10.4 months [8]. The ongoing phase II/III SWOG S2303 (PARAMUNE) trial is assessing the efficacy and safety of adding nivolumab to RAM+PTX compared with RAM+PTX alone in patients with advanced-stage gastric and esophageal cancers with PD-L1 CPS ≥1 [17]. To the best of our knowledge, our study is the first retrospective analysis comparing the efficacy of second-line RAM+PTX versus RAM+PTX plus nivolumab. Despite the absence of a statistically significant clinical benefit with the addition of an ICI, we observed numerically higher ORR, DCR, and median OS in the RAM+PTX plus nivolumab group. The lack of statistical significance may be partly explained by the small sample size and the fact that only 50% of the patients in the RAM+PTX plus nivolumab group had PD-L1 CPS ≥1, as the benefit of adding nivolumab appears to be primarily confined to patients with PD-L1 CPS ≥1 in the previous phase I/II study [7]. The median PFS was numerically lower in the RAM+PTX plus nivolumab group than in the RAM+PTX group. This may be partly explained by the modest ORR of 30%, as ICIs may prolong PFS by inducing durable responses in a subset of patients, and by the small sample size in this cohort. This finding might also reflect assessment-time bias because unscheduled early imaging (e.g., due to adverse events or comorbidities) could have led to the earlier documentation of progression than planned.

In our study, older age (≥50 years) and the presence of ascites were identified as independent poor prognostic factors for OS. These findings are consistent with those of previous studies. The exploratory analysis of the RAINBOW trial demonstrated that the median OS was shorter in patients with ascites (median OS for the RAM+PTX group: 7.2 vs. 11.4 months) [18]. However, the efficacy of the RAM+PTX combination was comparable between patients with and without ascites [18]. Similarly, in a real-world study, Chen et al. reported that the presence of ascites was associated with worse OS in both the RAM monotherapy group (median OS: 3.9 vs. 6.8 months) and the RAM+PTX group (median OS: 7.3 vs. 15.5 months) [19]. Our results support previous evidence indicating that the presence of ascites before RAM+PTX treatment is a poor prognostic factor.

In our cohort, we observed higher rates of grade ≥3 anemia and thrombocytopenia in real-world practice than in clinical trials [13]. Moreover, thromboembolic events, gastrointestinal perforation, and fistula formation were more frequent in our cohort. These findings underscore the importance of close clinical monitoring to enable early detection and management of potentially life-threatening adverse events associated with RAM+PTX combination.

Limitations

This study has several limitations. The primary limitations of this study are the small sample size in the second-line treatment arms and the retrospective, single-center design. Currently, RAM and ICIs are not reimbursed for second-line treatment of advanced gastric/GEJ cancers in Türkiye, which largely explains the limited number of patients who could receive these combinations. Nevertheless, our real-world data

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may serve as supportive evidence for future prospective studies in this patient population, where therapeutic options remain limited.

CONCLUSION

In conclusion, the real-world efficacy of RAM+PTX as second-line therapy in advanced gastric/GEJ cancers is consistent with the results of pivotal randomized trials. However, grade ≥3 TRAEs were more frequent in clinical practice. Although the addition of an ICI did not yield a statistically significant benefit, the ORR and DCR numerically improved. Further prospective studies, particularly in patients with PD-L1–positive tumors, are needed to clarify the potential benefit of adding an ICI. Moreover, RAM+PTX (±ICI) appears to be a reasonable third-line treatment option for patients with preserved performance status.

Ethics Committee Approval: The Ethics Committee of Koç University approved this study (Approval ID: 2025.096.IRB2.044, February 26, 2025).

Informed Consent: The study was retrospective, informed consent was not required from the patient.

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Conflict of Interest: The authors have no competing interests to declare.

Author Contributions: B.K: Conceptualization, Methodology, Formal Analysis, Software, Validation, Writing – Original Draft Preparation, Writing – Review & Editing; C.İ.K: Formal Analysis, Investigation, Writing – Review & Editing; F.K: Formal Analysis, Investigation, Writing – Review & Editing; N.D: Formal Analysis, Investigation, Writing – Review & Editing; Ö.A: Conceptualization, Methodology, Visualization, Writing – Review & Editing; Ş.L: Conceptualization, Methodology, Visualization, Writing – Review & Editing; F.S: Conceptualization, Methodology, Visualization, Supervision, Project Administration, Writing – Review & Editing.

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Safe analgesic alternatives in patients with NSAID-exacerbated respiratory disease: The role of tramadol and celecoxib

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MAIN POINTS

- Celecoxib and tramadol were well tolerated by all patients with N-ERD.
- Both agents showed significantly lower adverse reaction rates compared with other analgesics.
- Negative skin tests alongside positive aspirin challenges indicate a non–IgE-mediated mechanism.
- Tramadol may be considered a safe alternative analgesic for patients with NSAID hypersensitivity.
- Individualized provocation testing remains essential prior to clinical use.

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ABSTRACT

Aim: This study aimed to determine which analgesic agents can be safely administered to patients with nonsteroidal anti-inflammatory drug–exacerbated respiratory disease (N-ERD) and to evaluate the safety of tramadol as a potential alternative.

Materials and Methods: A total of 51 patients (34 females, 17 males; mean age 39.5 ± 14.2 years) with a history of NSAID hypersensitivity were retrospectively analyzed. All patients underwent oral drug provocation tests with celecoxib, paracetamol, nimesulide, meloxicam, and tramadol. In patients with a history of hypersensitivity to a single NSAID, negative skin test results were followed by an oral aspirin challenge to confirm N-ERD. Reaction rates among analgesics were compared using Cochran's Q test, followed by Dunn–Bonferroni pairwise analysis. A p-value <0.05 was considered statistically significant.

Results: Eleven patients (21.6%) had hypersensitivity to a single NSAID; all demonstrated negative skin test results but positive aspirin challenge outcomes, indicating a non–IgE-mediated mechanism. Celecoxib and tramadol showed significantly lower reaction rates compared with nimesulide, paracetamol, and meloxicam (p<0.001). More than half of the cohort (52.9%) required moderate- or high-dose inhaled corticosteroids, while 25.5% of patients with severe asthma were receiving biologic therapy.

Conclusion: Celecoxib and tramadol were well tolerated in all patients with N-ERD, suggesting that these agents are safe and effective analgesic alternatives. Individualized evaluation and supervised provocation testing remain essential to ensure safety before clinical use.

Keywords: Celecoxib, Nonsteroidal anti-inflammatory drug–exacerbated respiratory disease, Safe alternative analgesic, Tramadol

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INTRODUCTION

In susceptible individuals with asthma, chronic rhinitis, or nasal polyposis, the administration of aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs) may trigger upper or lower airway symptoms. These reactions typically present with nasal obstruction, watery rhinorrhea, sneezing, cough, wheezing, dyspnea, or, in severe cases, bronchospasm; systemic manifestations such as urticaria, angioedema, gastrointestinal discomfort, or hypotension may also occur [1,2].

This condition has historically been described using various terms—such as Samter's triad, Widal syndrome, and aspirin-sensitive asthma—but the designation *NSAID-Exacerbated Respiratory Disease (N-ERD)* is now widely accepted in clinical and academic practice [3]. Current guidelines classify NSAID hypersensitivity into four major phenotypes: NSAID-induced cutaneous reactions, NSAID-exacerbated cutaneous disease, NSAID-exacerbated airway disease, and single-agent–induced cutaneous reactions [4,5].

The underlying pathophysiology of N-ERD primarily reflects dysregulated arachidonic acid metabolism rather than IgE-mediated allergy. In most patients, inhibition of cyclooxygenase-1 (COX-1) alters eicosanoid balance and promotes leukotriene-driven airway inflammation, resulting in characteristic respiratory symptoms [6]. In contrast, single-agent reactions may involve drug-specific IgE but are far less common.

Given the clinical burden associated with N-ERD and the high frequency of analgesic requirements in this population,

identifying safe and well-tolerated alternatives to traditional NSAIDs is essential. This study aimed to determine which analgesics can be safely used in patients with N-ERD and to evaluate the safety of tramadol as a potential alternative option.

MATERIALS AND METHODS

Study design and participants

This retrospective study included 51 patients who were evaluated for suspected NSAID hypersensitivity between 2024 and 2025 at the Department of Allergy and Immunology. Eligible participants had a documented history of hypersensitivity to at least one NSAID, whereas individuals with incomplete medical records were excluded. Ethical approval was granted by the İnönü University Medical Ethics Committee (Decision No: 2025/8382, Date: 30 September 2025). All procedures adhered to the Declaration of Helsinki, and written informed consent was obtained from each participant.

Drug provocation protocol

All provocation tests were performed under continuous supervision by an allergist, with full emergency preparedness including access to resuscitation equipment and emergency medications. Baseline assessments—including physical examination, peak expiratory flow (PEF), blood pressure, and heart rate—were obtained prior to each dose. Testing was conducted between 09:00 and 12:00, and patients were monitored until 17:00 if no reaction occurred or until complete recovery in cases of a positive response. Incremental doses were administered at 30-minute intervals.

Patients with a history of hypersensitivity to a single NSAID first underwent skin testing to evaluate possible IgE-mediated mechanisms. If the skin test was negative, an oral aspirin challenge was performed to determine whether the reaction pattern represented true single-drug hypersensitivity or cross-intolerance consistent with N-ERD.

After determining the aspirin challenge outcome, oral provocation tests were conducted with alternative analgesic agents, including celecoxib (a selective COX-2 inhibitor), paracetamol, nimesulide, meloxicam (partial COX-2 inhibitors), and tramadol (a centrally acting opioid analgesic with low dependency potential).

A negative aspirin challenge indicated drug-specific hypersensitivity or limited cross-reactivity, permitting cautious substitution with alternative agents. Conversely, a positive reaction confirmed NSAID-exacerbated respiratory disease (N-ERD) or broad COX-1 cross-intolerance, necessitating strict avoidance of all COX-1 inhibitors. This structured, stepwise protocol enabled individualized risk assessment and evidence-based selection of safe analgesics. The diagnostic and management algorithm for evaluating NSAID hypersensitivity is presented in Figure 1.

Table 1. Demographic and clinical characteristics of the patients (n = 51).

Parameter	Value
Age (years), mean ± SD	39.5 ± 14.2
Female / Male	34 (66.7%) / 17 (33.3%)
Asthma	47 (92.2%)
Chronic rhinosinusitis with nasal polyps	38 (74.5%)
Moderate/high-dose inhaled corticosteroids	27 (52.9%)
Receiving biologic therapy	13 (25.5%)
Hypersensitivity to a single NSAID	11 (21.6%)
Positive aspirin provocation test	51 (100%)

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA). Categorical variables were presented as numbers and percentages, and continuous variables as mean ± standard deviation (SD).

Because each patient underwent multiple analgesic provocation tests, reaction rate comparisons were conducted using Cochran's Q test, which is appropriate for repeated categorical measurements within the same subjects. When Cochran's Q indicated statistical significance, pairwise comparisons were performed using Dunn's post-hoc test with Bonferroni correction.

A post-hoc power analysis was performed using G*Power version 3.1.9.7 based on the observed effect size (Cohen's w = 0.41). Using $\alpha = 0.05$, a confidence level of 0.95, and a sample size of 51, the achieved power ($1-\beta$) was 0.87, indicating sufficient statistical power to detect medium-to-large effect size differences. A p-value < 0.05 was considered statistically significant.

RESULTS

Among the 51 patients included in the study, 17 (33.3%) were male and 34 (66.7%) were female, with a mean age of 39.5 ± 14.2 years. Allergic rhinitis was present in 21 patients (41.1%), chronic urticaria in 17 patients (33.3%), and atopy in 24 patients (47%). Demographic and clinical characteristics are summarized in Table 1.

According to the Global Initiative for Asthma (GINA) classification [7], 27 patients (52.9%) were receiving step 4 or 5 treatment. Thirteen patients (25.5%) met the criteria for severe asthma, and among these, 4 were treated with omalizumab, 4 with mepolizumab, and 5 with benralizumab. Eleven patients (21.6%) reported a reaction to a single NSAID. All single-NSAID reactions showed negative skin test results but positive oral aspirin challenge outcomes, confirming a non–IgE-mediated cross-intolerance pattern. Eight patients required aspirin desensitization due to recurrent nasal polyps.

The most frequently implicated culprit NSAIDs were dexketoprofen (n = 36), diclofenac (n = 22), and ibuprofen (n = 14).

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Table 2. Drug challenge test results

Drug Tested	Type of Inhibitor	Positive n (%)	Observed Reactions
Celecoxib	Selective COX-2 inhibitor	0 (0%)	None
Tramadol	Non-NSAID analgesic	0 (0%)	None
Nimesulide	Partial COX-2 inhibitor	6 (11.7%)	Dyspnea, urticaria, nasal congestion
Meloxicam	Partial COX-2 inhibitor	4 (7.8%)	Wheezing, urticaria, rhinitis
Paracetamol	Weak COX-1 inhibitor	3 (5.8%)	Dyspnea, rhinitis, urticaria

Abbreviations: COX, cyclooxygenase; NSAID, nonsteroidal anti-inflammatory drug.

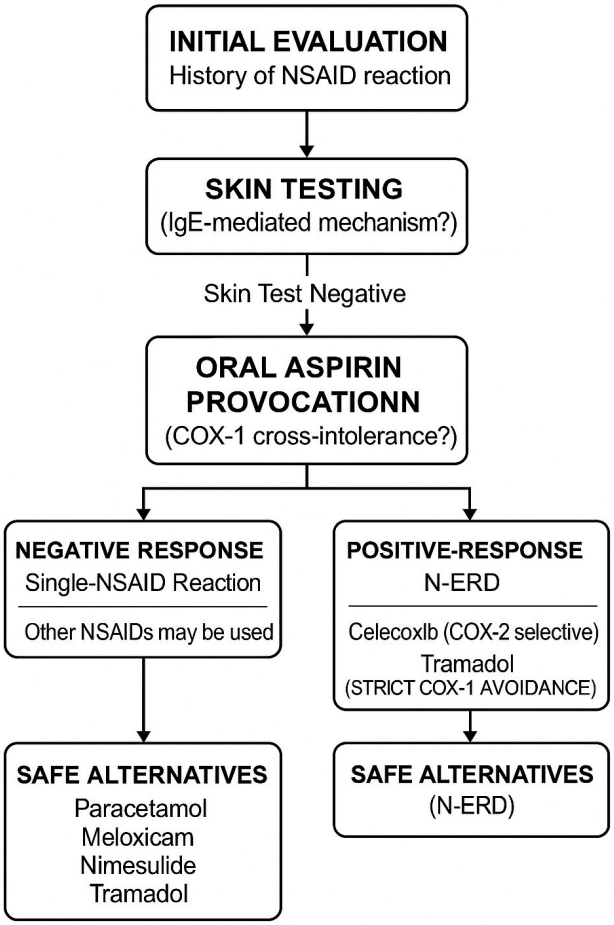

Figure 1. The diagnostic and management algorithm for evaluating NSAID hypersensitivity.

Drug Provocation Outcomes

Celecoxib and tramadol were tolerated by all patients undergoing provocation testing. In contrast, partial COX-2 inhibitors such as nimesulide, meloxicam, and paracetamol elicited significantly higher reaction rates.

Overall comparison of reaction frequencies among tested analgesics using Cochran's Q test demonstrated a significant difference ($p<0.001$). Post-hoc pairwise analyses using the Dunn–Bonferroni method showed that celecoxib and tramadol had significantly lower reaction rates than nimesulide, paracetamol, and meloxicam ($p<0.001$ for all comparisons). The detailed provocation outcomes are presented in Table 2.

DISCUSSION

In this study, all 11 patients who initially reported hypersensitivity to a single NSAID demonstrated negative skin test results but positive aspirin challenge outcomes. This finding suggests that these reactions were not IgE-mediated but instead reflected COX-1–related cross-intolerance [8]. Clinically, this is an important observation: even patients who appear to react to only one NSAID may have underlying NERD, and objective aspirin provocation remains essential for accurate classification [8].

The universal positivity of the aspirin challenge in this subgroup also highlights a major diagnostic pitfall. Without provocation testing, these individuals could be misclassified as "single-drug reactors," potentially leading clinicians to assume a drug-specific IgE mechanism. Our results emphasize that single-NSAID histories should not be equated with true selective allergy and that broad cross-reactivity remains likely unless proven otherwise [8–10]. This has significant implications for analgesic selection and long-term management.

Consistent with current evidence, none of the patients reacted to celecoxib. Selective COX-2 inhibitors are well known for their high tolerability in NERD, and our findings support celecoxib as a reliable and safe analgesic when COX-1 inhibitors must be avoided. The complete absence of reactions in our cohort aligns with previously reported tolerability rates [11–16], reinforcing celecoxib as the preferred first-line alternative.

Tramadol also demonstrated excellent tolerability. Although opioids rarely provoke respiratory reactions in NERD, pseudoallergic responses can occur, particularly with morphine or codeine. A prior study reported codeine reactions in 7.3% of NERD patients [13], underscoring the need for caution when selecting opioid analgesics. The absence of tramadol reactions in our population supports its role as a practical and safe option, especially when non-opioid analgesics are contraindicated or poorly tolerated.

The clinical characteristics of our cohort are consistent with the established NERD phenotype. More than half of the patients required moderate-to-high-dose inhaled corticosteroids, and nearly one-third were receiving biologic therapy, underscoring the heavy disease burden associated with NERD [17–20]. As in previous studies, chronic rhinosinusitis with nasal polyps—a hallmark of NERD—was common and severe, suggesting that patients frequently require inter-

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ventions that may increase the likelihood of analgesic exposure [21,22].

These findings collectively highlight the real-world challenge of pain management in patients with NERD. Because many analgesics carry a substantial risk of cross-reactivity, safe alternatives must be identified through structured, supervised testing. Our results show that celecoxib and tramadol can reliably serve this purpose.

Limitations

This study has some limitations, including its retrospective design and relatively small sample size. However, the uniform tolerability findings observed for both celecoxib and tramadol provide clinically meaningful guidance for everyday practice. Larger prospective studies incorporating molecular phenotyping could help clarify patient subgroups and further refine individualized analgesic strategies. Overall, our findings add to the growing evidence supporting the safety and practicality of celecoxib and tramadol for patients with NERD confirmed by provocation testing.

CONCLUSION

Celecoxib and tramadol were well tolerated by all patients with NSAID-exacerbated respiratory disease in this cohort, indicating that these agents may serve as safe and practical analgesic options when NSAID avoidance is required. The universal positivity of aspirin challenge among single-NSAID reactors underscores the importance of objective testing to accurately classify hypersensitivity patterns and guide individualized treatment. Although our findings support the use of celecoxib and tramadol in routine clinical practice, supervised drug provocation testing remains essential to confirm tolerability on a patient-specific basis. Larger prospective studies are needed to further validate these observations and refine evidence-based analgesic strategies for this challenging population. These findings support incorporating celecoxib and tramadol into standardized analgesic algorithms for patients with N-ERD.

Ethics Committee Approval: Ethical approval was obtained from the İnönü University Health Sciences Scientific Researchs Ethics Committee (Decision No: 2025/8382, Date: 30 September 2025).

Informed Consent: Written informed consent was obtained from each participant.

Peer-review: Externally peer-reviewed.

Conflict of Interest: The author declares no conflicts of interest.

Financial Disclosure: This research received no external funding.

Artificial Intelligence Disclosure: I would like to clarify that I used ChatGPT (OpenAI, GPT-4 version) only to help improve the English language of the manuscript. It was used for grammar correction and to make some sentences clearer and more fluent. It was not used for designing the study, analyzing data, interpreting results, selecting references, or developing any scientific conclusions. All scientific ideas, clinical interpretations, and the overall content of the manuscript were prepared entirely by me. I carefully reviewed and edited all suggested language changes myself before submission. I take full responsibility for the accuracy, originality, and integrity of the manuscript. I confirm that the use of AI was limited to language editing and is in line with the journal's ethical policies.

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The role of autism symptoms on eating behavior in children diagnosed with attention deficit hyperactivity disorder: A preliminary study

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MAIN POINTS

- Subclinical autistic traits are significantly associated with disordered eating behaviors in children with ADHD.
- Food fussiness is significantly higher in children with ADHD who also exhibit autistic traits than in those without autistic traits.
- The findings underscore the importance of a dimensional approach to clinical assessment, moving beyond categorical diagnoses.

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ABSTRACT

Aim: The literature highlights the overlap between Attention-Deficit/Hyperactivity Disorder (ADHD) and Autism Spectrum Disorder (ASD), yet the impact of subclinical autistic traits on feeding behavior in ADHD populations remains underexplored. This study aims to investigate eating behaviors in children diagnosed with ADHD compared with those of typically developing peers, and to assess how elevated autistic traits influence eating behaviors within the ADHD group.

Materials and Methods: A cross-sectional comparative design was employed, involving 67 children with ADHD and 75 healthy controls. Data were collected using the Children's Eating Behavior Questionnaire (CEBQ) and the Social Responsiveness Scale (SRS). Within the ADHD group, participants were stratified by the presence of autistic traits. Group comparisons and correlational analyses were conducted to examine associations between autistic traits and feeding behaviors.

Results: Compared with controls, children with ADHD exhibited significantly higher Desire to Drink scores and lower Emotional Under-Eating scores. Within the ADHD group, those with autistic traits had significantly higher Food Fussiness scores than those without autistic traits. Correlation analyses revealed significant associations between total SRS scores and multiple CEBQ subscales, including Emotional Overeating, Desire to Drink, Satiety Responsiveness, and Food Fussiness. Subscales, such as Pathognomonic Autistic Behaviors and Reciprocal Social Behavior, were especially predictive of disordered eating patterns.

Conclusion: Findings suggest that autistic traits---even at subclinical levels---are significantly associated with maladaptive eating behaviors in children with ADHD. These results emphasize the importance of transdiagnostic approaches in clinical assessments, moving beyond categorical diagnoses. Understanding the dimensional interplay between ADHD symptoms and autistic traits may improve early nutritional interventions and individualized treatment strategies.

Keywords: Autism spectrum disorder, Attention-deficit/hyperactivity disorder, Children, Eating behavior, Subclinical traits, Social responsiveness

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INTRODUCTION

Attention Deficit/Hyperactivity Disorder (ADHD) is characterized by symptoms of inattention, hyperactivity, and impulsivity that are inconsistent with the individual's age and developmental level. In contrast, Autism Spectrum Disorder (ASD) is defined by impairments in social communication, restricted interests, and repetitive behavioral patterns [1]. Although ADHD and ASD have historically been conceptualized as distinct conditions, converging neurobiological and genetic findings highlight shared etiological mechanisms between ADHD and ASD. Both disorders involve disruptions in large-scale neural circuits responsible for executive functioning, reward processing, and sensory regulation, supporting a dimensional rather than strictly categorical conceptualization of neurodevelopmental symptoms [2,3].

Clinical observations and epidemiological data further support this overlap. This overlap is not limited to full syndromal comorbidity but also encompasses subclinical traits. Studies report that 59–83% of children with ASD exhibit clinically significant ADHD symptoms, while 30–60% of children with

ADHD display autistic-like traits [4,5]. Moreover, some individuals may exhibit pronounced autistic features without fully meeting the diagnostic criteria for ASD. These features, often referred to as "subclinical autistic traits," include milder yet clinically meaningful difficulties in social reciprocity, flexibility, sensory modulation, and communication [6]. Increasing evidence indicates that these traits exert measurable effects on children's emotional, behavioral, and regulatory functioning, even in the absence of a formal ASD diagnosis. A transdiagnostic, dimensional framework is therefore essential for understanding how these overlapping features shape clinical presentations [3]. These autistic traits may play a particularly significant role in complex domains such as feeding behavior, where sensory sensitivities, emotional regulation, and behavioral inflexibility intersect.

Feeding behavior represents a complex domain frequently impaired in both ADHD and ASD, attracting growing research interest regarding its underlying neurocognitive mechanisms [7,8]. In individuals with ADHD, impulsivity, heightened reward sensitivity, and inattention contribute to maladaptive eating patterns such as emotional overeating, a preference for rapidly consumed, high-calorie foods, irregular meal routines, and difficulty maintaining attention during meals [9–14]. Executive dysfunction may further impair the recognition of internal hunger and satiety cues, leading to behaviors such as prolonged mealtimes or forgetting to eat [9,15]. In ASD, feeding difficulties are typically driven by sensory hypersensitivity (e.g., aversions to specific textures, smells, or temperatures), cognitive rigidity, insistence on sameness, and strict mealtime routines, leading to food selectivity, limited dietary variety, and increased caregiver stress. Gastrointestinal symptoms, which are more prevalent in ASD, may further complicate feeding patterns [16–19].

Critically, when ADHD and ASD symptomatology co-occur, even at subclinical levels, the impact on eating behavior appears to be more severe than in either condition alone [20–22]. For example, sensory hyperreactivity linked to autistic traits can intensify food fussiness, while ADHD-related impulsivity and reward-driven eating may contribute to emotional overeating or an excessive preference for palatable foods. Cognitive rigidity associated with autistic traits may restrict dietary variety, whereas ADHD-related disinhibition may promote inconsistent mealtime behaviors. Despite strong theoretical justification for these interaction effects, existing research has largely excluded diagnostically complex cases or focused solely on categorical ASD–ADHD comorbidity, leaving the contribution of subclinical autistic traits insufficiently examined [23,24].

This study was designed to address the identified gap by pursuing two primary objectives: first, to compare the eating behaviors of drug-naïve children with ADHD with those of typically developing peers; second, to investigate whether varying levels of autistic traits (low vs. high) within the ADHD group are associated with distinct feeding patterns. By incorporating a dimensional assessment of autistic symptomatology, the study moves beyond categorical diagnostic boundaries and responds directly to the need for transdiagnostic approaches. This methodology provides a clear framework for elucidating how cross-diagnostic features shape eating behaviors in children with ADHD. Ultimately, the findings aim to enrich the limited literature on this topic and to offer a novel, clinically relevant perspective by focusing on symptom severity, which may, in turn, inform more individualized interventions and nutritional counseling strategies.

MATERIALS AND METHODS

Participants and procedure

This study was designed as a preliminary, cross-sectional, comparative investigation. This study was reviewed and approved by the Non-Interventional Clinical Research Ethics Committee of Recep Tayyip Erdoğan University on June 13, 2024 (Decision No: 2024/135). Written informed consent was obtained from the parents of all participating children. The study was conducted in accordance with the principles of the Declaration of Helsinki. Participants were recruited from children presenting to the Child and Adolescent Psychiatry Outpatient Clinic of Recep Tayyip Erdoğan University Training and Research Hospital between July 2024 and February 2025. The ADHD group consisted of 67 drug-naive children aged 6–12 years who met the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) diagnostic criteria for ADHD. Drug-naïve status was confirmed through multiple sources, including detailed parental interviews, review of electronic medical records, and verification that no stimulant or non-stimulant ADHD medications (e.g., methylphenidate, atomoxetine) had ever been prescribed. Diagnoses were established by a child and adolescent psychiatrist using clinical interviews, academic performance records, teacher reports, and standardized psychometric evaluations. A total of 85 children were initially screened. Following comprehensive evaluation, 18 children were excluded due to atypical autism (n = 2), intellectual disability (n = 2), or incomplete parent/teacher questionnaire forms (n = 14).The final ADHD sample comprised 67 eligible participants. The control group included 75 typically developing children aged 6–12 years with no history of neuropsychiatric disorders or chronic medical conditions, evaluated as psychiatrically healthy through structured clinical interviews. The ADHD and control groups were matched on age and major sociodemographic variables to ensure comparability.

All participating children provided assent and written informed consent was obtained from their parents. Each child was administered a Sociodemographic Data Form, the Children's Eating Behavior Questionnaire (CEBQ), and the Social Responsiveness Scale (SRS). All scales were completed by the children's parents.

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Assessment tools

Sociodemographic data form: This form includes basic information such as the participant's age, gender, grade level, and parental education levels.

All participants were evaluated for psychiatric comorbidity by a specialist in child and adolescent psychiatry using the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version, Turkish Adaptation (K-SADS-PL-DSM-5-T) [25]. The K-SADS-PL-DSM-5-T is a comprehensive interviewer-administered assessment tool that allows evaluation of 23 diagnostic categories.

The Children's Eating Behavior Questionnaire (CEBQ), developed by Wardle and colleagues, is a 35-item parent-reported instrument that uses a five-point Likert scale to assess children's appetite characteristics and various eating behaviors [26]. Higher scores indicate more frequent expression of the related behaviors (e.g., food responsiveness, emotional overeating, food fussiness). The original internal consistency coefficients of the scale range between 0.74 and [upper bound missing]. 0.91. In the Turkish adaptation, internal consistency coefficients were reported to range from 0.61 to 0.84 for the subscales and 0.69 for the total scale [27].

The Social Responsiveness Scale (SRS) is a 65-item parent-report measure that assesses their child's social interactions and responsiveness over the past six months. It consists of five subscales: social awareness, social cognition, social communication, social motivation, and autistic mannerisms. Higher scores reflect greater impairment in social functioning. The scale has been shown to be significantly associated with autism diagnoses and is widely used to assess autistic traits [28,29]. Although a Turkish validation study has not yet been published, a large-

A scale study conducted by Ünal and colleagues on school-aged children reported a Cronbach's alpha of 0.86 and a test-retest reliability coefficient, Pearson r = 0.53 (p = 0.001) [30]. The total SRS scores range from 0 to 195. Scores between 60 and 80 indicate mild-to-moderate impairment in social reciprocity, while scores above 80 reflect severe impairment. In this study, children with SRS scores of 80 or higher were categorized into the "ADHD with autistic traits" group, whereas those with lower scores were categorized into the "ADHD without autistic traits" group.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics version 25.0. The Shapiro–Wilk test was used to assess the normality of continuous variables. For normally distributed variables, means and standard deviations were reported; for non-normally distributed variables, medians with minimum and maximum values were reported. In comparisons between the ADHD and control groups, independent t-tests were used for normally distributed continuous variables (e.g., height), Fisher's exact test for categorical variables (e.g., gender), and Mann–Whitney U tests for non-normally distributed variables. The ADHD group was further subdivided into two subgroups based on the presence or absence of autistic traits, and the same statistical methods were applied for between-subgroup comparisons. To assess the relationship between the CEBQ subscales and the SRS total and subscale scores in the ADHD group, Spearman's correlation analysis was conducted. Only CEBQ subscales showing statistically significant correlations with SRS scores were subsequently included in the generalized linear model (GLM) analyses. To determine whether autistic traits independently predicted eating behaviors after accounting for potential confounders, age and sex were included as covariates in all multivariable GLMs. Because the CEBQ subscale scores displayed a non-normal, positively skewed distribution, a Gamma A distribution with a log link function was used in these models. A p-value of less than 0.05 was considered statistically significant for all analyses.

RESULTS

A total of 67 children diagnosed with ADHD and 75 age-matched healthy controls were included in the analyses. The groups did not differ significantly in age, height, weight, or BMI (all p>0.05). However, gender distribution differed significantly between the groups, with a higher proportion of boys in the ADHD group (Table 1).

No significant differences between groups were observed on the eating-behavior subscale scores: Enjoyment of Food, Emotional Overeating, Satiety Responsiveness, Slowness in Eating, Food Fussiness, and Food Responsiveness (p>0.05). However, the Desire to Drink score was significantly higher in the ADHD group. Conversely, the Emotional Under-Eating subscale was significantly higher in the control group. Regarding social functioning, the ADHD group scored significantly higher on the SRS total score and its subscales Reciprocal Social Behavior, Social Use of Language, and Pathognomonic Autistic Behaviors, compared with the control group. These differences were statistically significant and are presented in Table 1.

Within the ADHD group, comparisons were made between those with autistic traits (n=12) and those without (n=55). No significant differences were found between these subgroups in terms of age, height, weight, or BMI. Although the gender distribution (6 males/6 females vs. 37 males/18 females) differed between groups, this difference was not statistically significant (p=0.211).

Regarding the subscales of eating behavior, no significant differences were observed between ADHD children with and without autistic traits in the domains of Enjoyment of Food, Emotional Overeating, Desire to Drink, Satiety Responsiveness, Slowness in Eating, Emotional Under-Eating, and Food Responsiveness (p>0.05). However, the Food Fussiness subscale scores were significantly higher in children with autistic traits. These results are presented in Table 2.

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Table 1. Comparison of demographic data and scale scores between the ADHD group and the control group.

Variable	ADHD (n = 67)	Control (n = 75)	p
Age	9 (7-14)	9 (7-13)	0.834*
Sex (Male/Female)	43 /24	33 / 42	**0.012****
Height (cm) (mean ± SD	132±10.8	133±11.2	0.337***
Weight (kg)	30 (20-70)	30 (18-60)	0.888*
BMI	17.7 (12.2-31.2)	17.2 (12.5-32.6)	0.378*
Enjoyment of Food	16 (6-25)	16 (6-25)	0.817*
Emotional Overeating	6 (4-19)	5 (4-14)	0.246*
Desire to Drink	10 (3-39)	6 (3-14)	<.001*
Satiety Responsiveness	20 (7-50)	19 (8-33)	0.874*
Slowness in Eating	8 (4-20)	8 (4-20)	0.329*
Emotional Under-Eating	9 (4-19)	11 (4-20)	**0.046***
Food Fussiness	7 (3-14)	8 (3-17)	0.122*
Food Responsiveness	10 (5-25)	8 (5-21)	0.150*
SRS-Reciprocal Social Behavior	40 (15-84)	35(21-60)	**0.009***
SRS-Social Use of Language	7 (0-17)	7 (2-12)	**0.046***
SRS-Pathognomonic Autistic Behaviors	16 (1-39)	9 (2-22)	**<.001***
SRS- Total Score	64 (16-127)	52 (27-80)	**<.001***

BMI: Body Mass Index, SD, standard deviation.SRS: Social Responsiveness Scale. Data are presented as median (minimum–maximum) or mean ± SD, as appropriate. Mann–Whitney U test unless otherwise stated; Fisher's exact test for sex; independent t test for height.

Table 2. Comparison of ADHD children with and without autistic traits

Variable	ADHD with Autistic Trait (n = 12)	ADHD without Autistic Trait (n = 55)	p
Age	10 (7-13)	9 (7-14)	0.278*
Sex (Male/Female)	6 M / 6 F	37 M / 18 F	0.211**
Height (cm) (mean ± SD	135.8±8.9	131.6±11.2	0.448***
Weight (kg)	32.5 (22-48)	30 (20-70)	0.572*
BMI	17.5 (14-21.6)	17.7 (12.2-31.2)	0.671*
Enjoyment of Food	15.5 (7-25)	16 (6-25)	0.600*
Emotional Overeating	8 (4-16)	6 (4-19)	0.274*
Desire to Drink	9 (3-39)	10 (5-15)	0.549*
Satiety Responsiveness	22.5 (15-32)	20 (7-50)	0.527*
Slowness in Eating	8.5 (4-15)	8 (4-20)	0.164*
Emotional Under-Eating	10.5 (7-15)	9 (4-19)	0.282*
Food Fussiness	9 (5-14)	6 (3-13)	**0.042***
Food Responsiveness	10 (5-25)	10 (5-25)	0.838*

BMI: Body Mass Index, SD, standard deviation.SRS: Social Responsiveness Scale. Data are presented as median (minimum–maximum) or mean ± SD, as appropriate. Mann–Whitney U test unless otherwise stated; Fisher's exact test for sex; independent t test for height.

Spearman correlation analyses examining the relationships between SRS subscales and eating behaviors revealed several significant associations. The Reciprocal Social Behavior subscale was positively and significantly correlated with Emotional Overeating (p=0.002), Desire to Drink (p=0.023), Emotional Undereating (p=0.004), and Food Fussiness (p=0.017). A positive correlation with Food Responsiveness (p=0.083) was also observed, though this did not reach statistical significance. The Social Use of Language subscale showed a significant positive correlation only with Emotional Under-Eating (p=0.011), whereas other correlations with eating behaviors did not reach statistical significance. The Pathognomonic Autistic Behaviors subscale was significantly and positively associated with Desire to Drink (p=0.016), Satiety Responsiveness (p=0.015), Emotional Under-Eating (p=0.015), and Food Fussiness (p=0.045). Although a positive correlation with Food Responsiveness was also noted, it did not reach statistical significance (p=0.385).

Finally, the total SRS score was positively and significantly correlated with Emotional Overeating (p=0.008), Desire to Drink (p=0.008), Satiety Responsiveness (p=0.039), Emotional Undereating (p<0.001), and Food Fussiness (p=0.018). The correlation with Food Responsiveness approached statistical significance (p=0.062). These findings are summarized in Table 3.

GLMs were conducted in the ADHD group (n=67) to examine the predictive power of subclinical autistic traits (SRS Total Score) on various CEBQ subscales, controlling for potential confounding variables, namely sex and age (gamma distribution with a log link

function). The results of the four separate GLM analyses revealed that the SRS Total Score significantly predicted three out of the four examined CEBQ subscales.

Satiety Responsiveness: The SRS total score was the strongest predictor ($\chi^2(1) = 7.069$, p=0.008). This finding indicates that an increase in the severity of autistic traits is associated

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Table 3. Correlation between CEBQ and SRS in the ADHD group.

Variable		Enjoyment of Food	Emotional Overeating	Desire to Drink	Satiety Responsiveness	Slowness in Eating	Emotional Under-Eating	Food Fussiness	Food Responsiveness	SRS-Reciprocal Social Behavior	SRS-Social Use of Language	SRS-Social Use of Language
Emotional Overeating	r	.294*										
	p	*(.016)*										
Desire to Drink	r	.290*	.338**									
	p	*(.017)*	*(.005)*									
Satiety Responsiveness	r	-.393**	.016	.254*								
	p	*(.001)*	(.898)	(.038)								
Slowness in Eating	r	-.029	.022	-.020	.114							
	p	(.815)	(.861)	(.873)	(.357)							
Emotional Under-Eating	r	.141	.377**	.283*	.261*	.236						
	p	(.255)	*(.002)*	*(.020)*	*(.033)*	(.055)						
Food Fussiness	r	.208	.132	-.005	-.163	-.158	-.104					
	p	(.092)	(.288)	(.968)	(.187)	(.201)	(.402)					
Food Responsiveness	r	.643***	.646***	581***	-.229	.021	.298*	.194				
	p	*(<.001)*	*(<.001)*	*(<.001)*	(.062)	(.868)	*(.014)*	(.116)				
Reciprocal Social Behavior	r	-.001	.375**	.278*	.206	.090	.350**	.290*	213*			
	p	(.991)	*(.002)*	*(.023)*	(.094)	(.469)	*(.004)*	*(.017)*	(.083)			
SRS-Social Use of Language	r	.061	.153	.204	.108	.067	310*	.012	214	.426***		
	p	(.621)	(.215)	(.097)	(.386)	(.590)	*(.011)*	(.923)	(.082)	*(<.001)*		
SRS-Pathognomonic Autistic Behaviors	r	.048	.150	294*	.295*	.004	295*	245*	.108	.634***	515***	
	p	(.700)	(.225)	*(.016)*	(.015)	(.976)	*(.015)*	*(.045)*	(.385)	*(<.001)*	*(<.001)*	
SRS- Total	r	.038	322**	321**	252*	.105	.395 ***	289*	.229	911***	624***	.860***
	p	(.762)	*(.008)*	*(.008)*	*(.039)*	(.396)	*(<.001)*	*(.018)*	(.062)	*(<.001)*	*(<.001)*	*(<.001)*

SRS: Social Responsiveness Scale, Correlation coefficients (r) and p-values (in parentheses) are shown *: p < .05, **: p < .01, ***: p < .001.

Table 4. Predictive power of subclinical autistic traits on CEBQ subscales: generalized linear model results in the ADHD Group.

Dependent Variable (CEBQ Subscale)	Omnibus Test χ^2(df)	Model p	Predictors	Wald χ2 p
Satiety Responsiveness	$\chi^2(3) = 7.802$	**0.05**	SRS Total Score	**0.008**
			Sex	0.372
			Age	0.291
Food Fussiness	$\chi^2(3) = 8.992$	**0.029**	SRS Total Score	**0.017**
			Sex	0.418
			Age	0.104
Desire to Drink	$\chi^2(3) = 10.766$	**0.013**	SRS Total Score	**0.016**
			Sex	**0.016**
			Age	0.324
Emotional Overeating	$\chi^2(3) = 5.535$	0.137	SRS Total Score	**0.057**
			Sex	0.217
			Age	0.418

CEBQ: Children's Eating Behavior.

with a significantly reduced response to satiety signals (i.e., lower Satiety Responsiveness scores). The overall model fit was at the boundary of marginal significance ($\chi^2(3) = 7.802$, p=0.050).

Food Fussiness: The SRS Total Score also significantly predicted Food Fussiness ($\chi^2(1) = 5.719$, p=0.017). This evidence established that increasing severity of autistic traits resulted in a significant increase in Food Fussiness behavior,

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which is related to sensory sensitivity and rigidity (Omnibus Test: $\chi^2(3) = 8.992$, $p = 0.029$).

The SRS Total Score was also found to have a significant independent effect on Desire to Drink ($\chi^2(1) = 5.792$, $p=0.016$). This behavior is associated with oral sensory seeking or excessive thirst, demonstrating that autistic traits influence behaviors in this domain as well.

Conversely, Emotional Overeating behavior was marginally predicted by the SRS Total Score ($\chi^2(1) = 3.608$, $p=0.057$), which falls just below the conventional threshold for statistical significance, suggesting a trend-level association between Emotional Overeating and autistic traits (Omnibus Test: $\chi^2(3) = 5.535$, $p=0.137$). Among the control variables included in the model, the effects of Age and Sex were generally non-significant. Age was not identified as a significant predictor of any of the four eating behaviors examined ($p>0.291$). Sex had a significant effect only on Desire to Drink ($\chi^2(1) = 5.753$, $p=0.016$), but not on the other three eating behaviors (Table 4).

DISCUSSION

This preliminary study aimed to compare the eating behaviors of children diagnosed with ADHD with those of healthy controls and to examine the impact of subclinical autistic traits on eating behaviors within the ADHD group. The findings indicate that ADHD is associated with specific alterations in eating behavior and that autistic traits—even below the diagnostic threshold—contribute meaningfully to feeding difficulties.

In the present study, the Desire to Drink score was significantly higher in the ADHD group, whereas Emotional Under-Eating was more prevalent in the control group. Previous literature has consistently reported a higher prevalence of abnormal eating behaviors in children with ADHD than in their typically developing peers [9,11]. Studies in preschool and school-aged samples show positive associations between ADHD symptoms and emotional overeating, desire to drink, food responsiveness, and irregular eating patterns [12,13].

Our finding of an increased Desire to Drink may reflect heightened reward sensitivity and impulsive reward-seeking, well-documented features of ADHD that often lead children to prefer rapidly consumed sweetened beverages [13,31]. Conversely, higher Emotional Under-Eating in the control group may suggest that children with ADHD are less responsive to internal emotional states during meals, potentially due to impaired interoceptive awareness and impulse control [11,32].

In the ADHD group, the SRS subscale scores were significantly higher, indicating that these individuals experience considerable difficulties in social functioning[28]. When individuals with ADHD were further stratified based on the presence of autistic traits, a significant difference emerged only in the *Food Fussiness* subscale. Food selectivity was more common among children exhibiting autistic traits [7,21]. This finding aligns with previous research suggesting that sensory sensitivities and a tendency toward routine—features commonly associated with ASD—may contribute to increased food selectivity [16,17,33].

The number of studies examining eating behaviors in ADHD–ASD comorbidity remains limited. Prior research has shown that children with both ADHD and ASD differ from typically developing peers in domains such as food responsiveness, enjoyment of food, satiety responsiveness, slowness in eating, and picky eating [21,22]. Our study differs in that it highlights similar disruptions even when autistic traits are subclinical, suggesting that the influence of autistic features on feeding behavior is dimensional and not restricted to formal ASD diagnoses.

Correlation analyses revealed that higher levels of autistic traits were associated with more pronounced eating problems, including emotional overeating, desire to drink, satiety responsiveness, emotional undereating, and food fussiness. These associations support the hypothesis that autistic traits contribute to dysregulated eating through mechanisms such as sensory processing atypicalities, social communication deficits affecting emotion regulation, and behavioral rigidity influencing dietary variety [17,34].

Previous research [7,35,36] has highlighted the role of sensory sensitivity — a diagnostic feature of ASD that is also frequently observed in children with ADHD — in contributing to food selectivity. The significant association between Emotional Under-Eating and both the total SRS score and all subscale scores mirrors findings from samples with ASD-only or ASD–ADHD comorbidity [12,21,22,34]; this study demonstrates that the same association holds in children with ADHD who exhibit subclinical autistic traits. Difficulties with emotion regulation, a commonly reported factor in both ADHD and ASD, are thought to underlie emotional eating behaviors [23,24].

The observed positive correlations between the Pathognomonic Autistic Behaviors subscale and the Satiety Responsiveness and Desire to Drink subscales may indicate a prominent role for hedonic hunger mechanisms in this population. This is a critical finding in terms of both increased obesity risk and reduced nutritional quality [9,37].

To directly test our primary hypothesis and control for confounding variables, GLM analyses controlling for the effects of sex and age were performed and provided evidence that subclinical autistic traits (SRS Total Score) are independent and significant predictors of several problematic eating behaviors in children diagnosed with ADHD (see Table 4). This finding supports the presence of a transdiagnostic mechanism, given the high comorbidity and dimensional overlap between ADHD and ASD [38]. Our analyses showed that the SRS Total Score significantly predicted three of the four primary eating behaviors: Satiety Responsiveness, Food Fussi-

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ness, and Desire to Drink.

The influence of autistic traits on eating behavior appears to be concentrated in two key areas. First, a significant negative effect on satiety responsiveness suggests that children with high autistic traits have an impaired ability to perceive and respond to satiety signals. The literature suggests that interoceptive awareness deficits, commonly reported in ASD [39], hinder appropriate regulation of eating in response to physiological cues in these children. Second, the positive effects on picky eating and drink cravings are consistent with sensory-seeking and sensory-avoidant behaviors frequently associated with ASD [36]. These children may be selective eaters because of hypersensitivity to the texture, temperature, or taste of foods, or they may engage in oral-gratification-seeking behavior (Drink to Desire). These findings indicate that autistic traits trigger eating problems in the ADHD population that are particularly related to sensory and physiological signal processing, whereas their contribution to emotion-regulation-related eating problems (emotional overeating) is marginal. Furthermore, the limited independent effects of the control variables (age and gender) on overall eating behavior — except for a significant effect of gender on 'Drink to Desire' — confirm that the observed effect is specific to the severity of autistic traits.

This study makes a valuable contribution to the limited literature exploring the relationship between ADHD and autistic traits in the context of eating behavior. It is among the few studies that specifically examine the influence of subclinical autistic traits on the feeding behaviors in children diagnosed with ADHD. While there is substantial literature on feeding behaviors in children with either ADHD or ASD, research addressing their comorbidity and overlapping symptomatology remains scarce. By evaluating autistic traits through a transdiagnostic lens and examining their behavioral implications, this study adopts an approach that more accurately reflects clinical reality and highlights the importance of features beyond categorical diagnoses. Furthermore, the inclusion of a healthy control group matched on age and sociodemographic characteristics enhances the comparative strength of the analysis and allows for contextual interpretation of feeding behavior deviations within the framework of neurodevelopmental disorders. Stratifying the ADHD group by SRS scores and conducting secondary analyses according to the presence of autistic traits add dimensional depth to the study. This enabled not only diagnosis-based evaluation but also interpretation based on symptom severity, clarifying the specific associations between autistic features and distinct eating behaviors.

This study, which presents a preliminary evaluation of the impact of eating behaviors and autistic traits in children diagnosed with ADHD, is subject to several methodological and sampling limitations. Notably, the number of participants in the ADHD group who exhibited autistic traits (n = 12) was relatively small compared to the rest of the sample. This may have limited the statistical power of subgroup comparisons and hindered adequate representation of variance. Given that this study was conceived as a preliminary investigation to explore initial patterns and guide future hypothesis-driven research, no a priori power analysis was conducted. As a result, the study may be underpowered to detect small-to-moderate effects, particularly in subgroup analyses. Furthermore, the sample was drawn from a single clinical center, which restricts the generalizability of the findings to the broader ADHD population. Longitudinal studies are necessary to assess how these variables influence one another over time. All assessment tools used in the study were parent-report questionnaires and therefore may be subject to systematic biases, including social desirability bias, recall bias and perceptual distortion. The absence of direct access to the child's internal experiences—particularly for insight-dependent behaviors like emotional eating—represents an important limitation. Additionally, autistic traits were classified based on SRS scores, and cases meeting the diagnostic criteria for ASD were excluded. Although participants were screened for ASD using diagnostic criteria, the SRS, while highly sensitive and valid, measures the severity of autistic traits rather than providing a diagnosis. Therefore, the clinical significance of intergroup differences must be interpreted with caution. Eating behaviors were assessed exclusively through questionnaire data. Apart from BMI, no other objective anthropometric measures, biochemical indicators (e.g., leptin and ghrelin levels), or dietary logs were collected, limiting the ability to relate findings to physiological outcomes. Lastly, there was a significant difference in gender distribution between groups.

CONCLUSION

In conclusion, this study suggests that autistic traits may significantly affect eating behaviors in individuals with ADHD. In recent years, there has been a growing body of research examining the relationship between ADHD, obesity, and disordered eating, with particular emphasis on the roles of neurobiological factors and emotional symptoms. On the other hand, the association between ASD symptoms and feeding behavior is well established. Given our findings, it becomes evident that clinical evaluations should not rely solely on categorical DSM diagnoses but should also account for spectrum-based traits, underscoring the importance of a transdiagnostic approach. Considering the high prevalence of co-occurring ADHD and ASD, understanding how these conditions interact in the context of feeding behavior is essential for designing more effective and developmentally timely intervention programs. Future longitudinal studies with larger and more diverse samples will be instrumental in establishing causal relationships and deepening our understanding of these complex interactions.

Ethics Committee Approval: Ethical approval for the research was obtained from the Non-Interventional Clinical Research

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Peer-review: Externally peer-reviewed.

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Age-related patterns of allergen sensitization and clinical phenotypes in adults with rhinitis

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MAIN POINTS

- Allergen sensitization among adults with rhinitis is characterized by a dynamic, age-dependent pattern, with sensitization rates declining with advancing age.
- Pollen and pet dander predominate among young adults, whereas mite sensitization persists and intensifies among middle-aged and older adults.
- The coexistence of asthma and urticaria becomes more frequent with advancing age and is often associated with sensitization to mites.
- Nearly one-third of sensitized adults exhibit complex polysensitization across multiple allergen groups, underscoring the heterogeneity of allergic disease.
- These findings highlight the importance of age-adapted diagnostic, preventive, and therapeutic strategies in adult allergic rhinitis.

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ABSTRACT

Aim: Allergic rhinitis (AR) is a common chronic condition that frequently coexists with asthma or urticaria. Allergen sensitization patterns vary by geography, environmental exposure, and age; however, data on adult and elderly populations remain limited. Understanding age-related sensitization trends is essential for optimizing diagnosis, prevention, and allergen immunotherapy (AIT) strategies.

Materials and Methods: This retrospective study included 1,982 adults diagnosed with rhinitis, drawn from 7,000 patients who underwent skin-prick testing at a tertiary allergy clinic in Türkiye. Patients were categorized by age as young (18–39 years), middle-aged (40–64 years), or elderly (≥65 years), and further classified according to clinical presentation as rhinitis alone, rhinitis with asthma, rhinitis with urticaria, or rhinitis with both asthma and urticaria. Polysensitization was defined as sensitization to ≥2 allergens, and complex polysensitization as sensitization across distinct allergen groups.

Results: Overall, 58.5% (n=1160) of patients demonstrated sensitization, with rates declining with age (62.0%, 52.7%, and 29.5%, respectively; p<.001). Among sensitized patients, 53.4% showed monosensitization and 46.6% showed polysensitization, of whom 63.3% exhibited complex patterns. Young adults, who most frequently presented with rhinitis alone (86.0%), were mainly sensitized to grass (29.5%), weed pollen (24.7%), and cat dander (13.0%); these rates were all significantly higher than those in middle-aged and elderly adults (p<0.01). Middle-aged and elderly adults, in contrast, showed significantly higher rates of mite sensitization than younger adults (up to 66.7%; p<.001 for both age groups). In these age groups, rhinitis was more frequently accompanied by asthma (10.3%) or urticaria (14.6%) (p<.01).

Conclusion: Allergen sensitization among adults with rhinitis demonstrates a dynamic, age-dependent pattern. Sensitization to pollen and pets predominates in younger adults, whereas sensitization to mites persists and intensifies with advancing age and comorbidities. These findings highlight age as a key determinant, whose effects are shaped by both immunologic and behavioral and environmental factors, underscoring the need for personalized, age-adapted approaches in allergy management.

Keywords: Allergic rhinitis, Allergen sensitization, Polysensitization, Asthma, Urticaria

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INTRODUCTION

Allergic rhinitis (AR) is one of the most prevalent chronic allergic disorders, affecting 10–40% of the adult population worldwide [1]. It is associated with significant impairment in quality of life, reduced work productivity, and frequent comorbidities [2]. Among these, asthma is a major comorbidity

and a significant risk factor among patients with rhinitis, reflecting their frequent coexistence and shared inflammatory mechanisms [3]. Urticaria, although not a classical comorbidity, may also coexist with rhinitis as an associated allergic condition. Prevalence studies indicate a significant overlap, which contributes further to disease burden [4].

Patterns of allergen sensitization exhibit substantial variability across environmental exposures, geographic regions, and age groups [5, 6]. While pediatric studies often report a predominance of pollen sensitization, adult studies sometimes emphasize sensitization to mites or molds. However, these patterns are not universal and may shift depending on geographic location or comorbidity status, such as asthma [6, 7]. Furthermore, data from large, longitudinal adult cohorts remain limited.

Another important clinical challenge is polysensitization, defined as sensitization to multiple, often unrelated, allergen groups [8]. Polysensitization and complex combinations, such as simultaneous pollen and indoor allergen reactivity, are frequently encountered in clinical practice and complicate therapeutic decisions, particularly in allergen immunotherapy (AIT) [9].

Despite the high prevalence and clinical impact of AR, there is a lack of large-scale studies systematically evaluating age-related differences in allergen sensitization among adults with rhinitis. Moreover, the interplay among rhinitis, asthma (its major comorbidity), and urticaria (an associated allergic condition) across different age groups has not been fully elucidated.

Therefore, this study aimed to analyze age-specific patterns of inhalant allergen sensitization in a large cohort of adult patients with clinically diagnosed rhinitis and to assess coexisting asthma and urticaria.

MATERIALS AND METHODS

Study design and population

This retrospective, single-center study was conducted at the Adult Allergy and Clinical Immunology outpatient clinic of Necmettin Erbakan University Faculty of Medicine, a tertiary referral hospital in Türkiye. Between 2022 and 2024, 7,000 adults underwent skin-prick testing (SPT) for suspected allergic diseases. Of these, 1,982 patients were diagnosed with rhinitis based on clinical history and physical examination and included in the analysis.

Study for ethical approval was obtained from the Clinical Research Ethics Committee of Necmettin Erbakan University (Approval No: 2025/5660). All procedures were carried out in accordance with the principles of the Declaration of Helsinki. Patient identities were anonymized, and data protection regulations were strictly observed.

Clinical assessment

The diagnosis of rhinitis was established based on clinical symptoms (nasal obstruction, rhinorrhea, sneezing, and/or itching) persisting for at least 12 months and supported by allergen sensitization results. Coexisting asthma and urticaria were identified based on medical history, physician diagnosis, and clinical documentation. Asthma was considered a major comorbidity of rhinitis, whereas urticaria was classified as an associated allergic condition.

Skin prick testing

SPT was performed using a standardized panel of inhalant allergens, from which the following were selected for evaluation: pollens (grass mix, tree mix, weed mix); mites (*Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*); mold (*Alternaria alternata*); cockroach (*Blattella germanica*); and pet dander (cat, dog). Histamine (10 mg/mL) and saline were used as positive and negative controls, respectively. A test was considered positive when the mean wheal diameter was at least 3 mm greater than that of the negative control after 15 minutes. All procedures were performed by trained allergy nurses under physician supervision.

Age grouping

Patients were categorized into three age groups: young adults (18–39 years), middle-aged adults (40–64 years), and older adults (≥65 years), consistent with commonly used epidemiologic classifications [10].

Definition of polysensitization and complex polysensitization

Polysensitization was defined as sensitization to two or more allergens on the skin-prick test panel. Complex polysensitization was defined as sensitization across different allergen groups, such as pollen, indoor arthropods (mites and cockroaches), mold, or pet dander.

Statistical analysis

Data were analyzed using IBM SPSS Statistics, version 22 (IBM Corp., Armonk, NY, USA). Descriptive statistics were presented as frequencies and percentages. Group comparisons were performed using chi-square tests. A p-value < 0.05 was considered statistically significant. All p-values were adjusted for multiple comparisons using the Bonferroni correction and are reported as adjusted p-values.

RESULTS

Study population

Of the 7,000 adults screened, 1,982 patients were clinically diagnosed with rhinitis and included in the analysis. The median age was 32 years (IQR 24–43), with 62% classified as young adults (18–39 years), 32% as middle-aged adults (40–64 years), and 6% as elderly adults (≥65 years).

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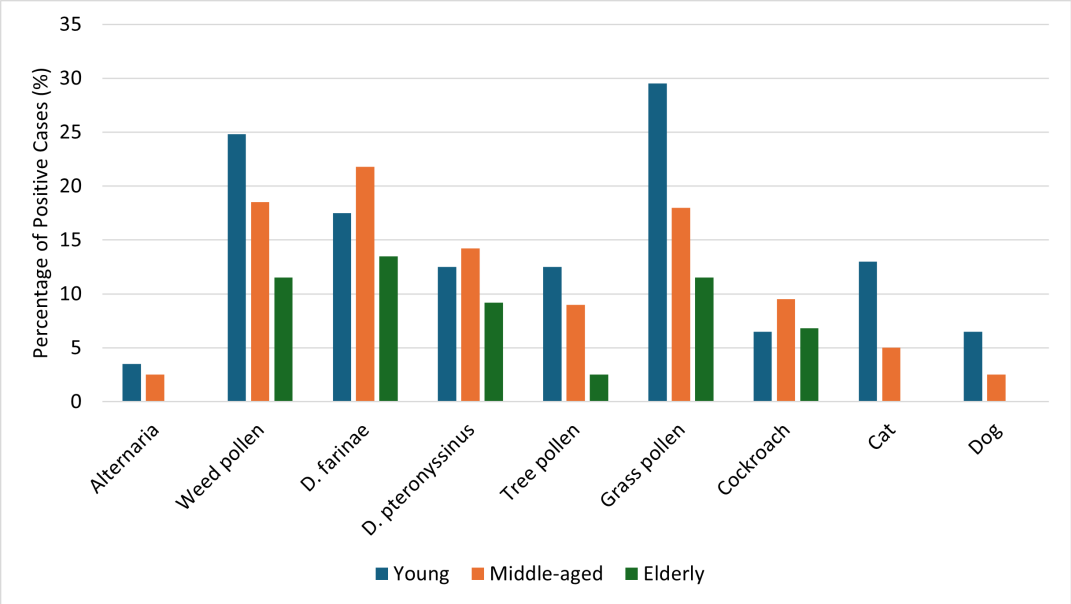

Figure 1. Age-related distribution of inhalant allergen sensitization in adults with rhinitis. Bars represent the percentage of positive cases for each allergen among young, middle-aged, and elderly adults. Red asterisks indicate statistically significant differences among age groups (Bonferroni-adjusted p<0.05).

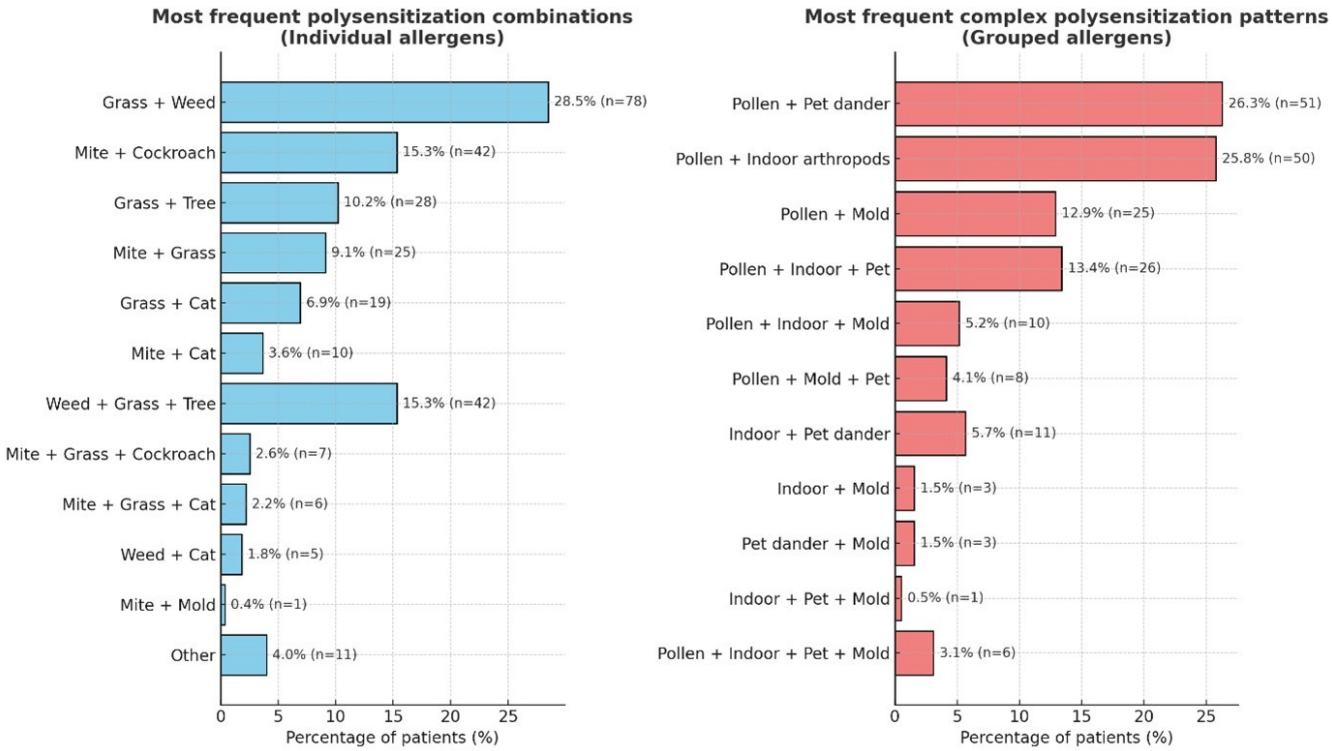

Figure 2. Distribution of allergen combinations among polysensitized patients based on individual allergens and grouped allergen categories. The left panel shows combinations based on individual allergens, and the right panel shows grouped combinations categorized as indoor arthropods (mites or cockroach), pollens (grass, tree, weed), pet dander (cat or dog), and molds (Alternaria). Bars indicate the percentage of patients, with the number of patients shown in parentheses.

Overall sensitization rates

Overall, 58.5% (n=1160) of patients demonstrated sensitization to at least one inhalant allergen. An age-related pattern emerged, with sensitization rates declining across age groups: 62.0% in young adults, 52.7% in middle-aged adults, and 29.5% in elderly adults (p<.001 for all pairwise comparisons). Among those sensitized, 620 individuals (53.4%) demonstrated monosensitization, indicating sensitivity to a single allergen. Polysensitization was present in 540 patients (46.6%). Of these, 342 (29.7% of all sensitized patients) demonstrated complex polysensitization, defined as sensitization across multiple distinct allergen groups. No significant

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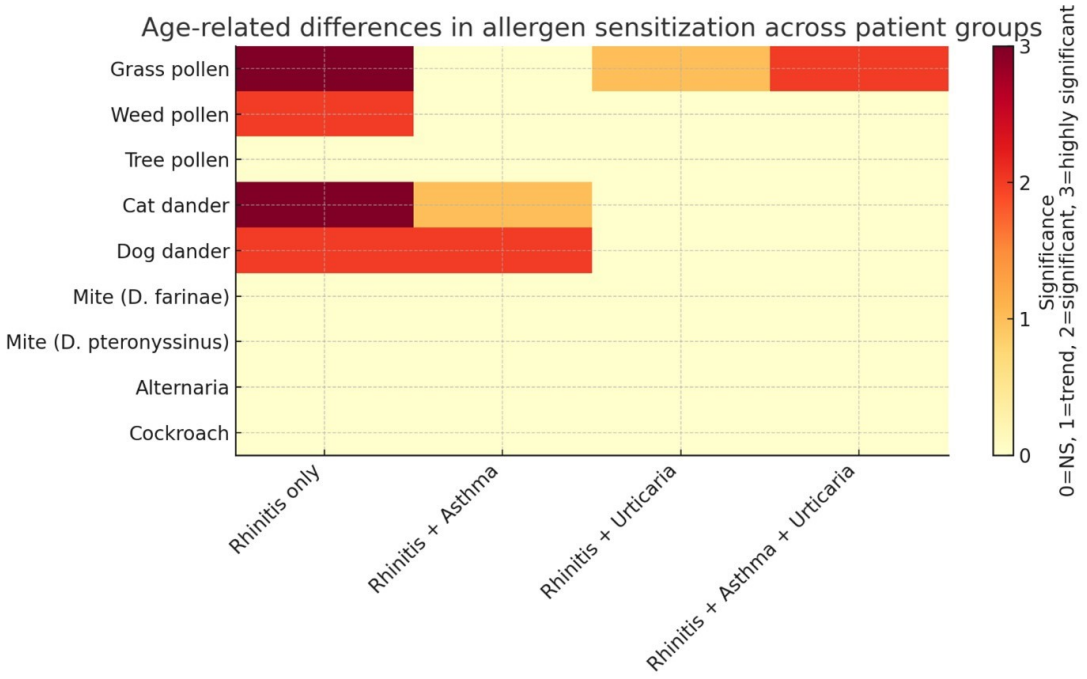

Figure 3. Age-related differences in allergen sensitization among patients with rhinitis, rhinitis with asthma, rhinitis with urticaria, and rhinitis with both asthma and urticaria. Heatmap colors indicate the level of statistical significance across age groups (0 = not significant, 1 = trend, 2 = significant, 3 = highly significant). Statistical significance indicated in the figure is based on Bonferroni-adjusted p values.

Table 1. Comparison of demographic and allergen sensitization characteristics across age groups.

Variable	Young adults (n=1352)	Middle-aged (n=586)	Elderly (n=44)	p-value	Age-related trend
Female	966 (71.4%)	385 (65.7%)	27 (61.4%)	.020	Young > Middle
Any sensitization	838 (62.0%)	309 (52.7%)	13 (29.5%)	<.001	Young > Others Middle > Elderly
Polysensitization	408 (48.2%)	129 (41.9%)	8 (61.5%)	0.13	NS
Complex polysensitization	262 (31.3%)	79 (25.6%)	6 (46.2%)	.09	NS

Values are presented as n (%). Adjusted post-hoc comparisons (Bonferroni correction) were applied. NS = not significant.

Table 2. Symptom distribution by age group.

Symptom Group	Young adults (n=1352)	Middle-aged (n=586)	Elderly (n=44)	p-value	Age-related trend (Bonferroni)
Rhinitis	1161 (86.0%)	426 (72.7%)	36 (81.8%)	<.001	Young > Middle
Rhinitis + Asthma	82 (6.1%)	60 (10.2%)	3 (6.8%)	.001	Middle > Young
Rhinitis + Urticaria	93 (6.9%)	85 (14.5%)	1 (2.3%)	<.001	Middle > Young
Rhinitis with both asthma and urticaria	14 (1.0%)	13 (2.2%)	4 (9.1%)	<.001	Elderly > Others
Unclassified phenotype	2 (0.1%)	2 (0.03%)	-	-	-

Values are presented as n (%). Bonferroni-adjusted post-hoc comparisons applied.

differences were observed across age groups (p=0.13 and 0.09, respectively). Baseline demographic and sensitization characteristics across age groups are summarized in Table 1.

Age-related allergen sensitization patterns

Age-specific analysis revealed distinct sensitization trends. Young adults exhibited significantly higher sensitization rates to grass pollen (29.5% vs. 18.8% vs. 13.6%, p< .001), weed pollen (24.7% vs. 18.6% vs. 11.4%, p= .001), cat (13.0% vs. 4.9% vs. 0%, p< .001), and dog (6.5% vs. 2.4% vs. 0%, p=.003) than those in the middle-aged and elderly groups. In contrast, sensitizations to house dust mites (*Dermatophagoides farinae* and *D. pteronyssinus*) and mold (*Alternaria*) did not differ significantly across age categories (p>0.05; Figure 1).

Age related mono- and polysensitization patterns

Among monosensitized patients (n=620), sensitization was most frequently directed against house dust mites (*Dermatophagoides pteronyssinus* and *D. farinae*; n = 260, 41.8%), followed by grass pollen (n=120, 19.3%) and cat dander (n=35, 5.6%). Other allergens, including tree pollen, cockroach allergens, mold, and dog dander, were observed in a small minority of patients. Sensitization to mites alone was significantly more frequent in middle-aged adults compared

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with young adults (36.3% vs. 24.5%, p=0.013), a difference primarily driven by *D. farinae* (p<0.001). Grass pollen was the second most common monosensitization pattern and significantly more frequent in young adults than in middle-aged adults (22.9% vs. 11.7%, p=0.007), while no significant differences were observed between the elderly and other age groups.

Among patients with polysensitization, the most frequent combinations of individual allergens were grass and weed pollens (28.5%), followed by mite and cockroach (15.3%) and weed, grass, and tree pollens (15.3%) (Figure 2, left). Age-stratified analysis showed that Pollen-based combinations predominated in young adults, whereas mite-plus-cockroach combinations were more common in middle-aged adults. Although the overall Chi-square test indicated a significant difference across age groups (p=0.045), the results should be interpreted with caution because of small cell counts.

When allergens were analyzed in grouped categories, the most common complex patterns were pollen with pet dander (26.3%) and pollen with indoor arthropods (25.8%), followed by pollen with mold (12.9%) and pollen with indoor arthropods plus pet dander (13.4%) (Figure 2, right). No significant differences were observed in the distribution of complex polysensitization patterns across age groups (p>.05).

Age-related distribution of clinical phenotypes and allergen sensitization patterns

When participants were stratified by clinical phenotype, distinct age-specific allergen sensitization profiles were observed, with significant differences across age groups highlighted in the heat map (Table 2, Figure 3).

Rhinitis alone

Rhinitis without comorbidities was more common in young adults than in middle-aged adults (86.0% vs. 72.9%, P_adj < .001). In this group, sensitizations predominantly involved grass (28.9% vs 17.1% vs 11.1%, $P_a$dj <.001), weed (25.1% vs 17.9% vs 5.6%, $P_a$dj =.001), and tree pollens (12.5% vs 9.0% vs 2.3%, $P_a$dj =.037), as well as cat (12.3% vs 4.2% vs 0%, $P_a$dj <.001) and dog dander (6.6% vs 2.6% vs 0%, $P_a$dj=.003), all of which were significantly more frequent in young adults. Among middle-aged adults with rhinitis alone, weed (17.9%) and grass (17.1%) represented the leading sensitizations, whereas in elderly adults *D. farinae* (13.9%) and grass pollen (11.1%) were most frequent (Table 2, Figure 3).

Rhinitis with asthma

The coexistence of rhinitis and asthma was more frequent in middle-aged adults than in young adults (10.3% vs. 6.1%; p=.001). In young adults with this phenotype, sensitizations to cat dander (12.7% vs 5.0%, p = .01) and dog dander (7.8% vs 2.3%, p=.005) were significantly more common. By contrast, in middle-aged adults, the most common sensitizations were to house dust mites (19.7% for *D. farinae*; 18.9% for *D. pteronyssinus*), followed by grass pollen (15.4%). Among elderly adults, sensitizations were again largely confined to house dust mites, with *D. farinae* (66.7%) and *D. pteronyssinus* (33.3%) constituting the only positive allergens identified (Figure 3).

Rhinitis with urticaria

The co-occurrence of rhinitis and urticaria was more common in middle-aged adults than in young adults (14.6% versus 6.9%; p<0.001). In this group, sensitizations were mainly directed against house dust mites (*D. farinae*, 50.6%; *D. pteronyssinus*, 31.8%) and grass pollen (27.1%), whereas cat (19.4% vs. 9.4%) and dog dander (7.5% vs. 1.2%) sensitizations were more common in young adults (p=.002 and p=.007, respectively). In older adults with rhinitis and urticaria, sensitizations were again confined to house dust mites (100% for both *D. farinae* and *D. pteronyssinus*; Figure 3).

Rhinitis with both asthma and urticaria

This phenotype was rare overall, but was more prevalent among elderly adults than in other age groups (9.1%, 2.2%, and 1.0%; p<0.001). In this group, sensitizations were largely limited to house dust mites (*D. farinae*, 22.7%; *D. pteronyssinus*, 20.5%), whereas sensitizations to pollen and animal dander were negligible (Figure 3). In contrast, cases of rhinitis with both asthma and urticaria were rare among young and middle-aged adults, and no consistent sensitization pattern was observed.

DISCUSSION

This large-scale study of approximately 2,000 adults with clinically diagnosed rhinitis characterizes age-related patterns of allergen sensitization and associated clinical phenotypes.

Our findings address this gap by demonstrating that allergen sensitization and disease expression in adults are not static but rather evolve with age, reflecting both environmental exposures and immunologic changes. Younger adults were more frequently sensitized to pollen and pet dander, typically presenting with isolated rhinitis, whereas middle-aged adults more often exhibited rhinitis accompanied by asthma or urticaria, with sensitization shifting toward house dust mites. Among elderly adults, sensitization patterns were almost exclusively limited to mites, while comorbid conditions frequently persisted. Across all age groups, polysensitization was common, and nearly one-third of sensitized patients demonstrated complex polysensitization involving multiple allergen groups, further highlighting the heterogeneity and evolving complexity of allergic disease in adulthood. Collectively, these results emphasize that age influences not only the prevalence but also the pattern and clinical complexity of allergic disease, underscoring the dynamic and multifactorial nature of allergen sensitization throughout adulthood.

Our findings showed that, with advancing age, comorbidities such as asthma and urticaria became more frequent, suggesting that chronic inflammation and long-term allergen ex-

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posure may sustain disease activity despite a general decline in sensitization diversity. Consistent with this, house dust mite sensitization remained stable and even became relatively more prominent in later decades, whereas sensitization to pollens and animal dander declined. These age-related shifts likely reflect the combined effects of immunosenescence, epithelial remodeling, and behavioral factors and are consistent with previous reports indicating persistence of sensitization to perennial allergens but waning of sensitization to seasonal allergens in older adults [11,12]. While this pattern may partly reflect immunologic mechanisms such as immunosenescence and reduced generation of new sensitizations, it may also be influenced by behavioral and environmental factors. Age-related remodeling of immune regulation—including reduced Th2 polarization, impaired dendritic cell function, and alterations in IgE memory responses—may weaken sensitization to newly encountered aeroallergens while maintaining reactivity to persistent indoor antigens such as mites [13,14]. In addition, lifestyle and environmental factors may reinforce these patterns, as younger adults are more likely to own pets and spend time outdoors, increasing exposure to pollen and animal dander, whereas middle-aged and elderly adults tend to remain indoors and have greater contact with dust mites. This concept is further supported by observations during the COVID-19 pandemic, when prolonged indoor confinement was associated with increased sensitization to indoor allergens such as mites and molds]15,16].

In younger adults, where pollens and animal dander are the predominant allergens, early recognition and timely initiation of immunotherapy may prevent disease progression and improve long-term outcomes. In clinical practice, as demonstrated in our study, dual positivity for grass pollen and cat dander is frequently observed in young adults with rhinitis. This pattern is generally interpreted as true co-sensitization rather than cross-reactivity, particularly when clinical manifestations are consistent with both exposures—such as worsening of symptoms during grass pollen seasons and persistence of symptoms indoors in households with a cat. Although cat removal is theoretically recommended to reduce allergen exposure, adherence to this measure remains low, with studies reporting implementation rates ranging from approximately 4% to 35% [17,18]. In these patients, conventional intranasal or systemic antiallergic therapy often provides suboptimal symptom control, underscoring the need for allergen-specific interventions. In co-sensitized adults, allergen immunotherapy remains effective when the clinically dominant allergen is targeted. However, robust evidence specifically addressing the outcomes of pollen immunotherapy in patients with a household cat and a concurrent clinically relevant cat allergy is scarce. Moreover, this coexistence may contribute to additive epithelial stress and

Inflammation occurs because both pollen and cat dander are known to induce innate oxidative and inflammatory responses in the airway epithelium [19]. The optimal management strategy for this frequently encountered co-sensitization pattern remains an open and largely unexplored area of research.

In middle-aged adults, asthma was more commonly associated with rhinitis, and mite sensitization was dominant, underscoring the central role of indoor allergen exposure in sustaining allergic airway disease. This pattern may reflect cumulative allergen exposure over time, as well as structural and immunologic remodeling of the airway epithelium, which could favor persistent sensitization to perennial allergens such as mites [20]. Similarly, in elderly adults, sensitization was largely confined to mites, while comorbid conditions such as asthma and urticaria frequently persisted in association with rhinitis [21,22]. Taken together, these findings suggest that early identification and mite-targeted management in middle-aged adults may not only improve symptom control at that life stage but may also help prevent the persistence or progression of comorbid allergic conditions in later decades. Furthermore, the present finding that mites were the most frequent allergens among monosensitized patients particularly when comorbid conditions are present—suggests that mite sensitization may represent a consistent and effective target for allergen immunotherapy across all age groups.

In our study, Polysensitization was observed in nearly half of the sensitized adults, with one-third of these individuals exhibiting complex patterns across multiple allergen groups. Comparable findings have been reported in a Korean adult cohort (prevalence of polysensitization, 41.3%), in a Finnish cohort (sensitization to more than three allergens observed in up to 56% of participants), and in a German cohort (polysensitization rates as high as 81%) [23-25]. The clinical importance of such broad sensitization profiles is further supported by multicenter data showing that increasing disease severity is linked to higher polysensitization rates, contributing to the heterogeneity of allergic rhinitis [26]. At the diagnostic level, discrepancies between skin prick testing and component-resolved diagnostics have been demonstrated, highlighting the need for molecular characterization in polysensitized patients [27]. Collectively, these findings indicate that polysensitization is both common and clinically relevant, and that precise molecular identification of the dominant allergen may be essential for optimizing diagnosis and therapy.

In Turkiye, studies of aeroallergen sensitization in adults have primarily reported the frequencies of common allergens, with pollens and house dust mites variably identified as the most prevalent sensitizing agents, even within studies conducted within the same geographic regions [28-30]. However, such frequency-based reporting alone provides limited insight into allergen–disease relationships. In a cohort from Şanlıurfa, Erbay demonstrated that while pollen sensitization was common among patients with allergic rhinitis, house dust mite sensitization was significantly more frequent in patients with isolated asthma [31]. Similarly, in the South Marmara region, Ediger et al. reported that pollen sensitization predominated

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in patients with rhinitis alone, whereas house dust mites were more frequent among those with concomitant rhinitis and asthma [29]. Our study expands this limited national literature by not only confirming phenotype-dependent sensitization patterns observed in previous studies, such as the predominance of house dust mite sensitization in patients with asthma, but also integrating age-stratified allergen sensitization, polysensitization profiles, and associated clinical phenotypes in a single, large adult cohort.

This approach allows for a dynamic and clinically relevant understanding of allergic disease that goes beyond simple prevalence reporting.

Limitations

Limitations of our study include its retrospective design, single-center setting, and reliance on skin prick testing without complementary molecular diagnostics such as CRD. The relatively small number of elderly patients also limits the generalizability of findings in this subgroup. Nevertheless, the large overall sample size, systematic age-stratified evaluation, and incorporation of comorbid allergic symptom profiles represent key strengths of this study.

CONCLUSION

This study demonstrates that allergen sensitization patterns and clinical phenotypes in adults are dynamic and age-dependent. Isolated rhinitis in young adults is primarily driven by pollen and animal dander, whereas mite sensitization predominates in middle-aged and older adults, and is often accompanied by asthma and urticaria. In this context, the high burden of polysensitization underscores the need for advanced diagnostic approaches and supports a more personalized, age-tailored strategy in allergy practice, integrating phenotypes and sensitization patterns to guide diagnostic, preventive, and therapeutic decisions.

Ethics Committee Approval: This study approval was obtained from the Necmettin Erbakan University Non-Interventional Research Ethics Committee (Approval No: 2025/5660).

Informed Consent: It was not deemed necessary due to the retrospective nature of the study.

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Evaluation of first-trimester PAPP-A and β-hCG levels in isolated single umbilical artery pregnancies and their association with adverse perinatal outcomes

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MAIN POINTS

- First-trimester PAPP-A levels below 0.65 MoM were significantly associated with adverse perinatal outcomes (CAPO) in isolated SUA pregnancies.
- β-hCG MoM levels were significantly higher in SUA cases compared to controls, but were not predictive of adverse outcomes.
- PAPP-A showed moderate predictive value (AUC=0.704) and may aid in risk stratification and closer third-trimester surveillance in isolated SUA cases.

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ABSTRACT

Aim: This study aimed to evaluate the association between first-trimester biochemical markers---pregnancy-associated plasma protein A (PAPP-A) and beta-human chorionic gonadotropin (β-hCG)---and adverse perinatal outcomes in pregnancies complicated by isolated single umbilical artery (SUA).

Materials and Methods: This retrospective case-control study was conducted at atertiary perinatology center between January 2023 and January 2025. The study group included 266 pregnant women diagnosed with isolated SUA, and the control group included 266 healthy singleton pregnancies. First-trimester serum PAPP-A and β-hCG MoM values were compared between groups. Composite adverse perinatal outcome (CAPO) was defined as the presence of at least one of the following: preterm birth, fetal growth restriction (FGR), oligohydramnios, polyhydramnios, intrauterine fetal demise (IUFD) or NICU admission.

Results: Although PAPP-A MoM levels were not significantly different between the SUA and control groups, PAPP-A values were significantly lower in SUA cases that developed CAPO ($p<0.001$). ROC analysis revealed that a PAPP-A cut-off <0.65 predicted CAPO with 71.2% sensitivity and 72.2% specificity (AUC=0.704, $p<0.001$). β-hCG MoM levels were higher in SUA cases than controls ($p<0.001$), but no significant difference was found between SUA cases with and without CAPO ($p>0.05$).

Conclusion: Low first-trimester PAPP-A levels may serve as a moderate predictor of adverse perinatal outcomes in isolated SUA pregnancies. PAPP-A may help guide risk stratification and antenatal surveillance intensity in this population.

Keywords: Single umbilical artery, Pregnancy-associated plasma protein-A, Beta-human chorionic gonadotropin, Pregnancy outcome

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INTRODUCTION

Single umbilical artery (SUA) is a condition in which the umbilical cord, which normally contains two arteries and one vein, contains only one artery and one vein [1]. After diagnosis, a detailed fetal anatomical scan should be performed [1,2]. SUA can occur either without any accompanying fetal anomalies (isolated SUA) or with accompanying anomalies. It is observed in approximately 0.5–1.3% of pregnancies [3,4]. SUA frequently coexists with genitourinary and cardiac anomalies [4,5]. In addition, it may also coexist with chromosomal anomalies [4]. Isolated SUA cases have been associated with perinatal outcomes such as low birth weight, preterm birth, and amniotic fluid abnormalities [3,6,7]. Although it is thought that pregnant women with isolated SUA can be monitored with routine obstetric follow-up in clinical practice, some approaches recommend increased fetal monitoring during the third trimester [7].

Pregnancy-associated plasma protein-A (PAPP-A) and the beta subunit of human chorionic gonadotropin (β-hCG) are important glycoproteins secreted by the placenta in early preg-

nancy [8]. PAPP-A begins to be secreted by trophoblasts after implantation, and its level continues to increase throughout pregnancy. Insufficient PAPP-A levels may reduce the effect of insulin-like growth factor, leading to impaired placental development and restricted fetal growth [8]. β-hCG is also a hormone secreted by syncytiotrophoblasts after implantation. It reaches its highest levels at the end of the first trimester and then gradually decreases [9]. High β-hCG levels are associated with increased trophoblast proliferation and invasion, while low β-hCG levels may indicate trophoblastic insufficiency. This condition may increase the risk of complications such as fetal growth restriction (FGR) in later weeks of pregnancy [9]. Recent studies have shown that PAPP- A and free β-hCG may be meaningful biomarkers for the early detection of various pregnancy complications [8,10,11].

Approximately two-thirds of SUA cases are isolated, with no accompanying structural or chromosomal abnormalities. Although isolated SUA is generally considered to have a better prognosis, recent evidence suggests that even in isolated SUA cases, the risk of certain complications due to placental insufficiency may be increased [3,12]. However, the number of studies specifically examining the relationship between first-trimester PAPP-A and β-hCG values in isolated SUA cases and subsequent perinatal outcomes is extremely limited. Therefore, this study aims to evaluate the perinatal prognostic significance of first-trimester biochemical markers in isolated SUA cases.

MATERIALS AND METHODS

This study is a retrospective case-control design conducted at a tertiary perinatology center where approximately 15,000 births occur annually, between January 2023 and January 2025. The study group consisted of women with singleton pregnancies who were diagnosed with isolated single umbilical artery (SUA) during detailed fetal anomaly screening at 20–24 weeks of gestation. The control group was selected from the database at a 1:1 ratio from healthy, structurally unanomalous singleton pregnancies with similar gestational characteristics following these patients. Ethical approval for the study was obtained from the Ankara Etlik City Hospital Scientific Research Evaluation and Ethics Committee No. 2 (decision number: AEŞH-BADEK2-2025/069 dated 13/05/2025). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Inclusion criteria were defined as being between 18 and 40 years of age, having completed first trimester screening tests between 11+0 and 13+6 weeks, and having complete perinatal records. Maternal systemic diseases, fetal aneuploidy or major congenital malformations, suspected congenital infection, tobacco or alcohol use, discontinuation of hospital follow-up, or incomplete data were accepted as exclusion criteria.

All ultrasound examinations, including the diagnosis of isolated single umbilical artery, were performed by experienced perinatologists at our tertiary center using standardized imaging protocols. Although examinations were conducted by more than one operator, formal interobserver variability analysis was not performed. All maternal, obstetric, and neonatal variables were obtained from the hospital's electronic information management system. In this context, maternal age, body mass index, gravida-parity information, obstetric and medical history, and pregnancy complications such as FGR, preterm delivery, amniotic fluid pathologies, and intrauterine fetal death that developed during pregnancy were recorded. First trimester biomarkers PAPP-A and β-hCG MoM levels were obtained from routine screening tests performed between 11+0–13+6 weeks, in accordance with national screening protocols.

Neonatal data included gestational age at delivery, mode of delivery, birth weight, ultrasound-based estimated fetal weight, 1- and 5-minute Apgar scores, neonatal intensive care unit (NICU) admission, and Composite Adverse Perinatal Outcome (CAPO). CAPO was defined as the presence of at least one of the following: preterm birth (<37 weeks), fetal growth restriction (birth weight <10th percentile), oligohydramnios, polyhydramnios, NICU admission, and intrauterine fetal death.

First-trimester serum PAPP-A and β-hCG levels were obtained from routine prenatal screening tests performed at the institutional laboratory using standardized automated immunoassay systems in accordance with national screening protocols.

The sample size was estimated a priori using G*Power software, assuming an alpha level of 0.05 and a statistical power of 80%, which indicated that a minimum of 116 participants per group would be sufficient. Ultimately, a total of 532 pregnancies were included in the study, comprising 266 isolated SUA cases and 266 healthy controls. The precision of the study findings is reported using effect estimates and their corresponding 95% confidence intervals, rather than post-hoc power calculations.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Macintosh, Version 25.0 (IBM Corp., Armonk, NY, USA). The distribution characteristics of continuous variables were assessed using the Kolmogorov–Smirnov test. Variables showing a normal distribution were defined as mean ± standard deviation, while variables not showing a normal distribution were defined as median (interquartile range). Student's t-test or Mann–Whitney U test was used for intergroup comparisons depending on the distribution characteristics. Categorical variables were expressed as numbers and percentages, and comparisons were made using Pearson's chi-square test or Fisher's exact test when appropriate. ROC curve analysis was performed to evaluate the predictive performance of first-trimester biomarkers, particularly PAPP-A MoM levels, for CAPO development in isolated SUA cases. The cutoff

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Table 1. Demographic and clinical characteristics of the groups.

	SUA group n=266	Control group n=266	p-value
Maternal age (years)	28.9±4.6	28.01±4.9	0.296[a]
Gravidity	2(2)	2(2)	0.256[b]
Parity	2(2)	2(1)	0.165[b]
BMI (kg/m^2)	30.94±4.8	30.05±4.9	0.793[a]
Gestational age at delivery (weeks)	38 (1)	39.1 (1.6)	**<0.001[b]**
Birth weight (g)	3006.9±475.4	3268.5±360.4	**<0.001[a]**
Cesarean section, n(%)	110 (41.3)	119 (44.7)	0.135[c]
Apgar score at 1st minute	9 (1)	9 (0)	**<0.001[b]**
Apgar score at 5th minute	10 (1)	10 (0)	**<0.001[b]**
Fetal growth restriction, n (%)	11 (4.1)	0 (0)	**<0.001[d]**
Preterm labor, n (%)	32 (12.0)	0 (0)	**<0.001[d]**
Oligohydramnios, n (%)	15 (5.6)	0 (0)	**<0.001[d]**
Polyhydramnios, n (%)	20 (7.5)	0 (0)	**<0.001[d]**
IUFD, n (%)	4 (1.5)	0 (0)	**<0.001[d]**
NICU admission, n (%)	25 (9.4)	34 (12.7)	0.226[c]
Composite adverse outcomes, n (%)	91 (34.2)	53 (19.9)	**<0.001[c]**

Data are expressed as n (%), mean ± SD, or median (interquartile range), where appropriate. A p value of <0.05 indicates statistical significance. Statistically significant values are in bold. a: Student's t test, b: Mann–Whitney U test, c: Pearson χ^2 test, d: Fisher's exact test (where appropriate). BMI: body mass index, IUFD: intrauterine fetal demise, NICU: neonatal intensive care unit.

value showing the best discriminatory power was determined using the Youden index. p<0.05 was accepted as the threshold for statistical significance in all analyses. Patients with missing data were not included in the analyses.

RESULTS

The demographic and clinical characteristics of the study population are summarized in Table 1. Maternal age, gravida, parity, and BMI did not differ significantly between the SUA and control groups (p>0.05). However, gestational age at delivery was significantly earlier in pregnancies with SUA (38.0 [1.0] weeks vs. 39.1 [1.6] weeks, p<0.001). Similarly, birthweight was significantly lower in the SUA group (3006.9±475.4 g vs. 3268.5±360.4 g, p<0.001). Several obstetric complications—including fetal growth restriction (4.1% vs. 0%), preterm labor (12.0% vs. 0%), oligohydramnios (5.6% vs. 0%), polyhydramnios (7.5% vs. 0%), and intrauterine fetal demise (1.5% vs. 0%)—occurred more frequently in the SUA group (all p<0.001). The 1st- and 5th-minute Apgar scores were also significantly lower among SUA pregnancies (p<0.001). NICU admission rates were similar between groups (p=0.226). Composite adverse perinatal outcomes were significantly more common in the SUA group (34.2% vs. 19.9%, p<0.001).

Table 2. Comparison of parameters used for first trimester screening in groups.

	SUA group n=266	Control group n=266	p-value
GA at screening (weeks)	12.1 (1)	12.1 (1)	0.996[b]
β-hCG MoM	1.08 (0.84)	0.80 (0.78)	**<0.001[b]**
PAPP-A MoM	0.97 (0.77)	0.97 (0.76)	0.308[b]
NT MoM	0.79 (0.17)	0.71 (0.26)	**<0.001[b]**

[b]: Mann-Whitney U, β-hCG: Beta-human chorionic gonadotropin, PAPP-A: Pregnancy associated plasma protein A, NT: Nuchal translucency, mom: A multiple of the median.

Table 3. Comparison of parameters used for first-trimester screening in SUA cases with andwithout adverse neonatal outcome.

	SUA group n=266	Control group n=266	p-value
GA at screening (weeks)	12 (0)	12 (1)	0.184[b]
β-hCG MoM	1.16 (0.74)	1.18 (1.84)	0.713[b]
PAPP-A MoM	0.63 (0.85)	1.19 (0.82)	**<0.001[b]**
NT MoM	0.77 (0.16)	0.79 (0.17)	0.830[b]

[b]: Mann-Whitney U, β-hCG: Beta-human chorionic gonadotropin, PAPP-A: Pregnancy associated plasma protein A, NT: Nuchal translucency, mom: A multiple of the median.

First-trimester screening parameters are presented in Table 2. The gestational age at the time of screening did not differ between groups (p=0.996). β-hCG MoM levels were significantly higher in the SUA group compared with controls (1.08 [0.84] vs. 0.80 [0.78], p<0.001). PAPP-A MoM values were comparable between groups (p=0.308). Nuchal translucency MoM, however, was significantly higher in the SUA group (0.79 [0.17] vs. 0.71 [0.26], p<0.001), indicating altered early fetal and placental characteristics in SUA pregnancies.

A comparison of SUA cases with and without composite adverse perinatal outcome is shown in Table 3. Screening gestational age and β-hCG MoM levels did not differ significantly between CAPO-positive and CAPO-negative SUA pregnancies (p>0.05). In contrast, PAPP-A MoM values were markedly lower in pregnancies that experienced CAPO (0.63 [0.85] vs. 1.19 [0.82], p<0.001). NT MoM values were similar between the groups (p=0.830). These findings suggest that lower first-trimester PAPP-A levels may serve as an early indicator of adverse perinatal outcomes in isolated SUA cases.

The diagnostic performance of first-trimester PAPP-A MoM

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Table 4. Diagnostic performance of first-trimester PAPP-A MoM levels for predictingcomposite adverse perinatal outcomes in isolated SUA pregnancies.

	Cut-off*	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI)	p-value
First trimester PAPP-A (MoM)	<0.65	71.2% (61.8--78.8)	72.2% (64.9--78.7)	63.3% (54.4-71.4)	78.8% (71.4-84.6)	0.704 (0.634-0.774)	**<0.001**

*Cut-off value determined by Youden's index. AUC: area under the curve; CI: confidence interval; PPV: positive predictive value; NPV: negative predictive value; PAPP-A: pregnancy-associated plasma protein A; β-hCG: betahuman chorionic gonadotropin; CAPO: composite adverse perinatal outcome; SUA: single umbilical artery.

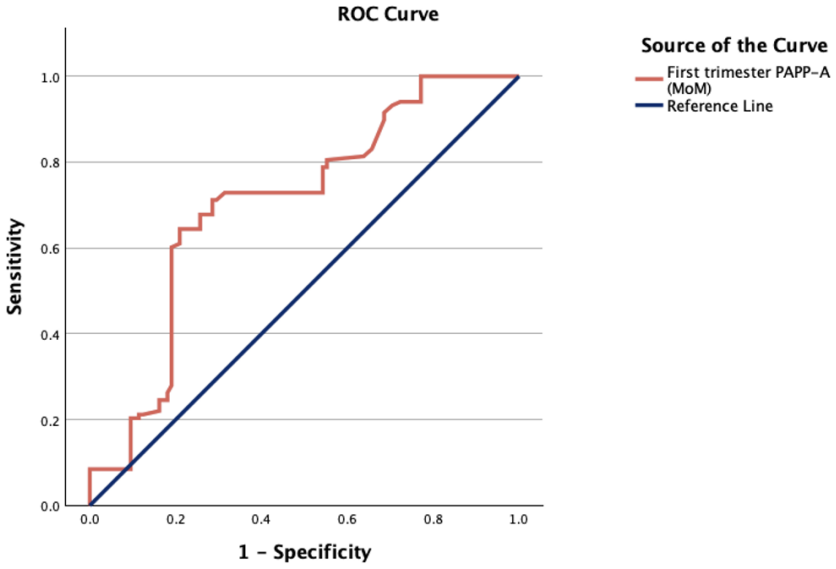

Figure 1. Receiver operating characteristic (ROC) curve for first-trimester PAPP-A levels inpredicting CAPO among pregnancies with SUA.

levels for predicting CAPO is presented in Table 4 and illustrated in Figure 1. ROC analysis demonstrated that a PAPP-A cutoff of <0.65 yielded a sensitivity of 71.2% and a specificity of 72.2%, with an AUC of 0.704 (95% CI: 0.634–0.774, p<0.001). These results indicate a moderate predictive capacity of first-trimester PAPP-A levels for identifying SUA pregnancies at increased risk for adverse perinatal outcomes. At the selected cut-off value (PAPP-A <0.65), the corresponding positive and negative predictive values were 63.3% and 78.8%, respectively.

DISCUSSION

This study investigated the importance of first-trimester screening parameters (β-hCG & PAPP-A) in predicting perinatal outcomes in patients diagnosed with isolated SUA. Isolated SUA usually progresses to delivery without complications. However, predicting which patients are at risk for poor perinatal outcomes can be very helpful to clinicians. In this regard, our study showed that low PAPP-A levels in patients with isolated SUA are associated with the development of CAPO (p<0.001). In the advanced analysis (ROC), it was shown that a PAPP-A MoM below 0.65 can predict CAPO with 71.2% sensitivity and 72.2% specificity (AUC=0.704), indicating that this biomarker has moderate predictive value from a clinical perspective. In contrast, although β-hCG MoM values were higher in isolated SUA cases compared to the control group, no significant difference was found between β-hCG levels in predicting CAPO development (p>0.05). These results suggest that PAPP-A levels in the first trimester may be a stronger marker for perinatal risk classification in isolated SUA pregnancies.

Although a statistically significant difference in NT MoM values was observed between isolated SUA pregnancies and controls, the measured values remained within the normal reference range. Therefore, this finding may not necessarily indicate a clinically relevant abnormality. Mild variations in NT measurements have been reported in association with placental or hemodynamic adaptations in early pregnancy, even in the absence of structural or chromosomal anomalies [13]. In isolated SUA cases, such subtle changes may reflect physiological variability rather than pathological processes. Nevertheless, the clinical implications of this finding are uncertain, and further prospective studies are needed to clarify its significance.

PAPP-A is a placenta-derived glycoprotein secreted by syncytiotrophoblasts and plays a critical role in placental development and fetal growth [14]. Low PAPP-A levels in the first trimester may be associated with insufficient trophoblast invasion and incomplete transformation of the uterine spiral arter-

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ies. These alterations may result in increased resistance in the uteroplacental circulation and chronic placental hypoperfusion. Consequently, reduced placental volume and impaired nutrient exchange may contribute to adverse outcomes such as fetal growth restriction [8,9]. Parallel to this mechanism, Turner et al. found that low PAPP-A levels were associated with preeclampsia, preterm birth, and low birth weight [14]. Similarly, Livrinova et al. also demonstrated a relationship between low PAPP-A and these pregnancy complications [15]. Pummara et al. also emphasized that the risk of preterm delivery is high in patients with low PAPP-A [16].

Morris et al. showed that low PAPP-A levels increased the development of CAPO by 3.31 times. In this large-scale meta-analysis, which included data from more than 175,000 pregnancies, it was emphasized that although low PAPP-A in the first trimester was significantly associated with complications such as preeclampsia and FGR, its positive predictive value alone remained low [17]. In our study, PAPP-A levels did not show a significant difference was observed between the control group and the isolated SUA group. However, when evaluating SUA cases individually, low PAPP-A levels were found to be associated with adverse perinatal outcomes. The AUC value of 0.704 obtained from the ROC analysis in our study is consistent with existing evidence indicating that PAPP-A has limited predictive power when used alone. However, PAPP-A may still be a valuable tool for identifying high-risk pregnancies among patients diagnosed with isolated SUA. Its clinical utility may be enhanced when used in combination with other clinical and biochemical parameters. In this context, first-trimester PAPP-A demonstrates a moderate discriminative performance (AUC = 0.704). Accordingly, PAPP-A may be a valuable adjunct for identifying high-risk pregnancies among patients with isolated SUA, particularly for early risk stratification and tailoring antenatal surveillance rather than serving as a standalone predictor.

In our study, mean first-trimester β-hCG levels in isolated SUA cases tended to be higher than in healthy pregnancies. The number of studies directly comparing first-trimester β-hCG values with SUA cases in the literature is quite limited. A study including 56 patients diagnosed with SUA or velamentous placenta (27 SUA, 29 velamentous placenta) reported that maternal serum β-hCG values may be relatively high compared to the control group [18]. The increase in β-hCG levels observed in isolated SUA cases may reflect enhanced trophoblast activity within the placenta as a compensatory response to the presence of a single umbilical artery [19]. This adaptive mechanism may stimulate syncytiotrophoblast function and lead to increased β-hCG secretion. In contrast, Tulek et al. found isolated SUA cases to be associated with low PAPP-A, but showed no significant difference in β-hCG levels [19]. A study published in 2023 showed that low initial β-hCG levels after transfer in IVF pregnancies were associated with subsequent placental abnormalities, and that the incidence of SUA was significantly higher in this group [20]. However, in that study, β-hCG levels were measured at the time of initial pregnancy detection rather than during the first-trimester screening period. Therefore, the discrepancy between their findings and ours may be attributable to differences in the timing of measurement.

In our study, β-hCG levels were not found to be significantly predictive of adverse perinatal outcomes in cases with SUA. This finding is consistent with the general consensus in the literature; the use of free β-hCG as a predictor of placental problems is unclear and has not been found to be reliable on its own [21]. Parry et al. showed that levels of many placental proteins, including β-hCG, in early pregnancy are associated with adverse pregnancy outcomes. However, they emphasized that these analytes alone are not sufficient to predict CAPO in regression models [22]. Although elevated β-hCG levels may be observed in isolated SUA cases, available data suggest that this finding alone is not indicative of poor perinatal outcomes. In conclusion, the current literature agrees that β-hCG changes observed in isolated SUA cases are largely due to placenta- derived physiological/pathophysiological mechanisms. Prospective studies are needed to better understand these mechanisms.

A strength of this study is that it focused exclusively on pregnancies with isolated single umbilical artery and compared them with a control group of pregnancies without identified structural anomalies. This approach allowed us to evaluate perinatal outcomes associated with isolated SUA while minimizing the influence of major confounding conditions. Previous studies investigating the relationship between isolated SUA and first-trimester biochemical markers such as PAPP-A and β-hCG are limited. In this context, our findings add to the existing literature by providing additional data on the potential association between these markers and adverse perinatal outcomes in isolated SUA pregnancies.

Nevertheless, the retrospective and single-center nature of this study represents an important limitation and may restrict the generalizability of the findings. In addition, although the diagnosis of isolated single umbilical artery was based on standardized ultrasound protocols and performed by experienced perinatologists, ultrasound-based assessment may be operator-dependent, and a formal evaluation of interobserver variability was not conducted. First-trimester biochemical markers were obtained from routine laboratory records, and therefore potential measurement variability related to laboratory conditions and assay performance cannot be entirely excluded. Furthermore, composite adverse perinatal outcome (CAPO) was used as a composite endpoint, and the relative contribution of each individual component may differ. Finally, although data regarding the association between isolated SUA and first-trimester biochemical markers such as PAPP-A and β-hCG remain limited in the literature, the proposed cut-off values derived from this study should be interpreted with caution. Therefore, prospective, multicenter studies with larger and more diverse populations are war-

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ranted to validate these cut-off values, confirm their clinical applicability, and establish robust evidence- based recommendations for the management of isolated SUA pregnancies.

CONCLUSION

This study demonstrates that low first-trimester PAPP-A levels in pregnancies complicated by isolated single umbilical artery are associated with an increased risk of adverse perinatal outcomes. Although the predictive performance of PAPP-A is moderate, it may serve as a useful adjunct for early risk stratification and guiding antenatal surveillance intensity in this population. In contrast, first-trimester β-hCG levels were not predictive of adverse perinatal outcomes in isolated SUA pregnancies. Further prospective, multicenter studies are warranted to validate these findings and clarify their clinical applicability.

Ethics Committee Approval: Ethical approval for the study was obtained from the Ankara Etlik City Hospital Scientific Research Evaluation and Ethics Committee No. 2 (decision number: AEŞH-BADEK2-2025/069 dated 13/05/2025).

Informed Consent: It was not deemed necessary due to the retrospective nature of the study.

Peer-review: Externally peer-reviewed.

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The mediatory role of coping styles in the relationship between mindfulness in parenting and burnout in mothers of children with autism spectrum disorder

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MAIN POINTS

- As the level of mindfulness in parenting increases among mothers of children with autism spectrum disorder (ASD), depersonalization — one dimension of burnout — decreases and the sense of personal accomplishment — another dimension — increases, thereby reducing overall burnout.
- Helpless and submissive coping styles mediate the protective effect of mindfulness in parenting on depersonalization. Mindfulness has a protective effect against depersonalization by reducing negative coping styles.
- The absence of a substantial direct correlation between mindfulness in parenting and the emotional exhaustion dimension of burnout may be explained by mindfulness exerting its influence on different dimensions of burnout through distinct mechanisms.
- The positive effect of mindfulness in parenting on personal accomplishment is direct: it strengthens the parent's sense of competence rather than altering coping strategies.
- Targeting negative coping styles in parenting interventions may increase the effectiveness of mindfulness-based approaches in reducing parental burnout.

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ABSTRACT

Aim: The purpose of this study was to examine the relationship between mindfulness in the mothers of children with autism spectrum disorder(ASD)and coping with stress styles and parental burnout, and to test the mediatory role of coping with stress styles.

Materials and Methods: The research was performed using a cross-sectional design. Seventy-one mothers of children with ASD were included in the study. The participants were administered the Mindfulness in Parenting Questionnaire, Ways of Coping Questionnaire, and Maslach Burnout Inventory. Relationships were examined using correlation analysis, and mediating effects were examined using the bootstrap method.

Results: Mindfulness in parenting exhibited a negative correlation with the burnout depersonalization subdimension (r = -0.337, p = .008) and a significant positive correlation with the personal accomplishment subdimension (r = 0.548, p < .001). Mediation analysis showed that the helpless approach (b= -0.045, BootSE=0.029, 95% BCa CI [--0.117, --0.003]) and submissive approach (b= 0.031, BootSE=0.018, 95% BCa CI [0.002, 0.073]) coping styles played a mediating role in the protective effect of mindfulness on depersonalization. However, coping styles did not have a statistically significant mediating role in the effects of mindfulness on emotional exhaustion or personal accomplishment.

Conclusion: The results suggest that mindfulness-based interventions may be effective in reducing burnout in mothers of children with ASD by targeting negative coping strategies. Therefore, integrating psychoeducational components into intervention programs to help mothers recognize nonfunctional coping styles is recommended.

Keywords: Autism spectrum disorder, Mindfulness in parenting, Parental burnout, Coping styles, Mediation analysis

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INTRODUCTION

The neurodevelopmental illness known as autism spectrum disorder (ASD) is typified by limited and repetitive behaviors as well as fundamental deficits in social communication [1]. Parents caring for children with ASD experience elevated psychological stress due to their children's intensive care needs and difficulties with communication and behavioral problems. Research has indicated that parents of ASD have notice-

ably higher levels of stress than parents of children with usual development [2]. Studies have also reported that the chronic stress experienced by the parents of ASD can lead to burnout in the long term [3].

Burnout has been defined as a three-dimensional structure resulting from chronic stress, its components being emotional exhaustion, depersonalization, and personal accomplishment [4]. Although burnout has traditionally been defined from an occupational perspective, the literature also considers it from a parental perspective, as parental burnout. The relevant literature largely focuses on burnout resulting from chronic stress specific to parenthood [3]. According to current research, mothers of children with ASD have higher levels of parental burnout than mothers of generally developing children [5,6].

In addition to stress levels in the context of parental burnout, how individuals cope with stress is also important. When an individual encounters a stressor, they evaluate its threat potential. If the event is perceived as exceeding the individual's resources, he will re-interpret it and endeavor to develop appropriate coping strategies [7]. Mindfulness affects cognitive evaluation in this process by allowing the individual to focus on current experiences in an open and non-judgmental manner, as well as permitting them to adopt more effective coping strategies [8].

Mindfulness is defined as focusing on the current situation with a non-judgmental and accepting approach [9]. Mindfulness in parenting involves understanding the child's needs in an empathetic manner, responding to behaviors with awareness, and adopting a more conscious presence in parent-child interactions [10]. Surprisingly, the number of studies examining the efficacy of mindfulness-based interventions aimed at preventing parental burnout is limited [11–13]. Parental stress and burnout can be decreased by mindfulness-based interventions aimed at parents who have kids with chronic illnesses, according to the findings of earlier research [11]. However, research on whether interventions aimed at increasing mindfulness have a direct or indirect effect on parental burnout is limited.

The term "coping" refers to behavioral and cognitive techniques used to balance internal and external demands on oneself when under pressure. Within the framework of the 'Mindful Coping Model' mindfulness suggests that individuals can regulate negative thoughts and emotions in a healthier manner and will adopt more adaptive coping strategies [7,14]. Studies involving health professionals and teachers have reported that mindfulness affects burnout via coping styles [15,16]. These findings suggest that mindfulness in parenting can indirectly affect burnout levels by shaping coping styles [11,17]. However, the psychological mechanisms underlying the positive impact of mindfulness, particularly the mediating role of coping styles within that relationship, have not been empirically investigated in mothers of children with ASD. Therefore, studies are needed to test this relational model in this special population. The aim of the current investigation is to close this gap in the literature.

Accordingly, this study aimed to examine the relationships among mindful parenting, coping styles, and dimensions of burnout in mothers of children with ASD. Additionally, we aimed to test whether coping styles statistically mediated these relationships.

MATERIALS AND METHODS

Study design and participants

The study used a cross-sectional design. The participants were mothers of children with ASD, aged 2-15, who presented to the child and adolescent psychiatry clinic and were identified using the consecutive sampling method. During the study period, all mothers and children who met the inclusion criteria and presented to the child and adolescent psychiatry clinic with an ASD diagnosis were assessed. Those who consented to participate were enrolled in the study. All participating children underwent DSM-5-TR-based psychiatric evaluations.

Exclusion criteria;

- The presence of any neurological, genetic, or metabolic disease in the participating children or siblings thereof,
- The presence of adults requiring care within the family,
- Children not living with their mothers,
- Mothers with severe psychiatric disorders who were unable to reliably complete the psychometric scales or who were receiving active treatment for these disorders were excluded from the study.

An analysis performed using G*Power 3.1 software revealed that the required minimum sample size was 55, based on a medium effect size ($f^2 = 0.15$), $\alpha = 0.05$, and 80% power. After applying the exclusion criteria, the study retained a sufficient sample size of 71 participants. The Alanya Alaaddin Keykubat University Clinical Research Ethics Committee approved the study (dated 26.03.2025; decision no. 06-03). Before the study started, the participants were informed of its purpose, and their verbal and written agreement was obtained.

Psychometric instruments

Data for the study were collected through face-to-face interviews with mothers when they presented at the clinic. The severity of the children's ASD was evaluated using the Childhood Autism Rating Scale (CARS). A sociodemographic data form, the Ways of Coping Questionnaire (WCQ), the Mindfulness in Parenting Questionnaire (MIPQ), and the Maslach Burnout Inventory (MBI) were administered to the children's mothers.

Childhood Autism Rating Scale: This behavioral scale was developed to evaluate the severity of symptoms in children with ASD [18]. Sucuoğlu et al. validated the scale's Turkish language version [19]. CARS consists of 15 domains; relationships to people, emotional response, adaptation to change,

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imitation, body use, object use, taste, smell, and touch response, visual response, listening response, verbal communication, non-verbal communication, fear or nervousness, activity level, level and consistency of general impressions, and intellectual response. The disease's severity is indicated by the overall score [18].

Ways of Coping Questionnaire: The Ways of Coping Questionnaire (WCQ) was originally developed by Folkman and Lazarus. This questionnaire assesses coping styles. The Turkish short version of the scale, adapted and validated by Şahin and Durak, consists of 30 items rated on a 4-point Likert scale [20]. The scale includes five subscales: Self-Confident Approach (SCA), Optimistic Approach (OA), Seeking Social Support (SSS), Helpless Approach (HA), and Submissive Approach (SubA). There are no reverse-scored items. Higher total scores indicate a greater use of the relevant coping style [20].

Mindfulness in Parenting Questionnaire: McCaffrey et al. created this 28-item Likert-type measure to assess mindfulness in parent-child interactions [10]. Gördesli et al. translated it into Turkish, using 24 items and two subdimensions from the validity and reliability study [21]. There is no cut-off point for the MIPQ. The total scale score and sub-dimension scores are used to assess mindfulness levels. The total scale score was employed in the present study. Higher total scores indicate higher mindfulness levels.

Maslach Burnout Inventory: The Maslach Burnout Inventory (MBI) is a 22-item Likert-type scale developed to measure individuals' levels of burnout [4]. The Turkish validity and reliability study of the MBI was conducted by Ergin et al [22]. Emotional exhaustion(MBI-EE),depersonalization(MBI-DP),and personal accomplishment(MBI-PA)constitute its three subscales. Positive responses were found on the personal accomplishment subscale, whereas negative responses were found on the emotional exhaustion and depersonalization subscales. There is no cut-off point for the MBI.

Statistical analysis

Descriptive statistics were expressed as frequencies, percentages, means, standard deviations, medians, and Q1-Q3 values. The Kolmogorov-Smirnov test was applied to determine whether normality assumptions were violated. Skewness and kurtosis analysis was performed, with values between -2 and +2 being regarded as indicating normal distribution [23]. Correlations were determined using Pearson's correlation test when normality assumptions were not violated; otherwise, Spearman's correlation analysis was used. Following the theoretical framework and preliminary analyses, a model was established in which MBI sub-dimension scores were the outcome variable and MIPQ scores were the predictor. The mediating effects of WCQ sub-dimensions were then examined in that model. Child age, maternal age, education, and employment status were included as control variables in the model. Bootstrapping, a non-parametric resampling procedure, is recommended for testing mediation that does not impose the normality assumption of the sample distribution [24]. The evaluation is robust to deviations from normality, and asymmetric confidence intervals were obtained by bootstrapping. The mediation analysis in this study was conducted using the PROCESS 4.2 beta in SPSS. The mediation models were tested using the bootstrap method. In these analyses, the mediation effect was considered statistically significant if no 0 value was present between the lower and upper limits of the 95% bias-corrected and accelerated confidence intervals (BCa CI) of the indirect effect (IE) obtained based on 5000 bootstrap sampling [25]. The analyses were conducted using IBM SPSS Statistics version 26.0 (Armonk, NY: IBM Corp.), and p-values below 0.05 were considered statistically significant.

RESULTS

Seventy-one participants were included in the research, of whom 76.1% were boys and 23.9% were girls. In terms of parental education, 40.8% of the mothers had an elementary-level education, and 59.2% had a high-school education or above. The majority of the participating mothers were employed (84.5%), while 15.5% were housewives. The detailed distribution of other demographic characteristics is presented in Table 1.

Descriptive statistics

Evaluation of MBI subscale scores across participants' sociodemographic variables revealed no significant differences in mean EE, PA, or DP scores by gender, maternal education, maternal employment status, paternal education, paternal employment status, monthly income, or family structure (Table 1).

The mean age of the children in the study was 7.06±6.0 years (range: 2-16). Descriptive statistics were calculated for the scales applied. These were evaluated using the the distributions of the results, skewness and kurtosis, and graphical methods (Table 2).

Correlation analyses

Correlation analysis was used examine relationships among variables. Accordingly, the MIPQ exhibited significant positive correlations with the SCA (r = 0.454, p < .001) and OA (r = 0.412, p= .001) stress-coping styles, and a significant correlation with SubA(r = -0.376, p = .003).MIPQ also exhibited a significant negative correlation with the DP burnout subdimension(r = -0.337, p = .008), and a significant positive correlation with PA (r = 0.548, p < .001). Correlation analysis between coping with stress styles and burnout subdimensions revealed a significant negative correlation between the EE dimension and OA (r = -0.358, p=0.002) and a significant positive correlation with HA (r = 0.352, p = .003). The PA dimension exhibited significant positive correlations with (r =

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Table 1. A comparison of Maslach burnout inventory subscale score distributions according to sociodemographic variables.

	N	%	Emotional Exhaustion		Personal Accomplishment		Depersonalization	
			Mean±SD/ Median (Q1-Q3)	p	Mean±SD/ Median (Q1-Q3)	p	Mean±SD/ Median (Q1-Q3)	p
Gender								
Female	17	23.9	7 (5-10)	0.71[b]	26 (24-28)	0.71[a]	3 (2-5)	0.83[b]
Male	54	76.1	6 (4-14)		25 (21.3-29)		3 (1-7)	
Maternal education								
Elementary	29	40.8	7 (4-11)	0.97[b]	24 (21-28)	0.99[b]	3 (1-7)	0.93[b]
High school or above	42	59.2	6 (4-13)		24 (24-30)		3 (1-6)	
Maternal employment status								
Housewife	11	15.5	7 (4-14)	0.26[b]	25 (22-29)	0.59[b]	3 (1-7)	0.41[b]
Working	60	84.5	5 (8-14)		25 (22-27)		1 (0.5-5)	
Paternal education								
Elementary	34	47.9	6 (4-10.8)	0.35[b]	25.1±4.74	0.76[a]	3 (0-6)	0.31[b]
High school and above	37	52.1	8 (4-13)		25.4±4.22)		3 (1-7)	
Paternal employment status								
Not working	5	7.1	4 (4-8)	0.28[b]	25 (25-29)	0.50[b]	4 (3-4)	0.63[b]
Working	65	92.1	7 (4-14)		26 (22-29)		3 (1-7)	
Monthly family income								
≤ MW	20	28.2	8.40±6.06		24.7±5.44		4.45±4.24	
2-3 MW	44	62	8.43±5.43	0.41[c]	25.2±4.09	0.49[c]	3.75±3.10	0.37[c]
≥ 4 MW	7	9.8	6.14±6.28		27.1±3.48		2.71±4.64	
Family structure								
Nuclear	62	91.2	7 (4-12.8)	0.57[b]	25.0±4.54	0.489[a]	3 (1-7)	0.89b
Extended	6	8.8	5 (3.5-8.25)		26.3±2.88		3 (2.25-3.75)	

[a]Student's t, [b]Mann Whitney U, [c]Kruskal Wallis, MW: Minimum wage.

Table 2. Descriptive statistics for ages and psychosocial scales.

		Mean±SD	Median (Q1-Q3)	Skewness	Kurtosis
Age (child)		7.06±6.00	6 (4.33-9.04)	-	-
Mother Age		36.91±8.95	36 (32-42)	-	-
Father Age		40.91±8.84	39 (36-45)	-	-
CARS		44.06±10,17	45 (35-53)	-	-
MIPQ		78.75±9.66	80 (72-85.3)	-0.483	-0.392
WCQ Subdimensions	SCA	23.93±2.88	24 (21.5-26)	-0.389	-0.415
	OA	16.10±2.49	16 (15-18)	-0.627	0.738
	HA	17.69±4.01	17 (15-20)	0.297	-0.076
	SubA	12.62±3.44	12 (10-15)	0.470	0.393
	SSS	11.89±1.92	12 (11-13)	-0.574	1.803
MBI Subdimensions	EE	8.20±5.65	7 (4-13)	0.596	-0.547
	PA	25.23±4.45	25 (22-29)	-0.325	-0.713
	DP	3.85±3.59	3 (1-6.5)	0.827	-0.110

MIPQ: Mindfulness in Parenting Questionnaire, WCQ: Ways of Coping Questionnaire, SCA: Self-Confident Approach, OA: Optimistic Approach, HA: Helpless Approach, SubA: Submissive Approach, SSS: Seeking Social Support, MBI: Maslach Burnout Inventory, EE: Emotional Exhaustion, DP: Depersonalization, PA: Personal Accomplishment.

0.382, p = .001) and OA (r = 0.377, p = .001), and significant negative correlations with HA (r = -0.249, p = .037) and SSS (r = -0.29, p = .014). The DP dimensions was powerfully negatively correlated with the OA and SCA coping with stress styles (r = -0.258, p = .03 and r = -0.465, p < .001, respectively). HA and DP showed a substantial positive correlation (r = 0.488, p <.001) (Table 3).

Mediation analyses

Mediation analyses were conducted in which MIPQ scores represented the predictor variable, MBI subdimensions represented the outcome variables, and coping-with-stress styles represented the mediator. Child age, maternal age, education, and employment status were included as control variables in the analysis.

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Table 3. Correlations between mothers' parenting mindfulness, coping strategies, and burnout levels.

		MIPQ	SCA	OA	HA	SubA	SSS	EE	PA	DP
MIPQ		---								
	SCA	0.454***	---							
	OA	0.412**	0.627***	---						
WCQ	HA	-0.242	-0.252*	-0.337**	---					
	SubA	-0.376**	-0.141	-0.063	0.405***	---				
	SSS	0.033	0.209	0.167	0.025	-0.072	---			
	EE	-0.211	-0.226	-0.358**	0.352**	0.210	-0.023	---		
MBI	PA	0.548***	0.382**	0.377**	-0.249*	-0.290*	0.178	-0.190	---	
	DP	-0.337**	-0.258*	-0.465***	0.488***	0.067	0.010	0.640***	-0.294*	---

*p<0.05, **p<0.01, ***p<0.001. CARS: Childhood Autism Rating Scale, MIPQ: Mindfulness in Parenting Questionnaire, WCQ: Ways of Coping Questionnaire, SCA: Self-Confident Approach, OA: Optimistic Approach, HA: Helpless Approach, SubA: Submissive Approach, SSS: Seeking Social Support, MBI: Maslach Burnout Inventory, EE: Emotional Exhaustion, DP: Depersonalization, PA: Personal Accomplishment.

Table 4. The mediatory effects of coping with stress styles in the relationship between mindfulness in parenting and burnout.

						Bootstrap BC at 95% CI for indirect effect		
Type	Predictor	Mediator	Outcome	b	SE	Lower	Upper	p
	MIPQ	SCA	DP	0.011	0.031*	-0.045	0.078	-
	MIPQ	OA	DP	-0.038	0.031*	-0.111	0.011	-
Indirect	MIPQ	SSS	DP	-0.001	0.006*	-0.014	0.011	-
	MIPQ	HA	DP	-0.045	0.029*	-0.117	-0.003	-
	MIPQ	SubA	DP	0.031	0.018*	0.001	0.073	-
Direct	MIPQ	-	DP	-0.093	0.047	-0.188	0.002	0.06
Total	MIPQ	-	DP	-0.134	0.043	-0.220	-0.049	0.003
	MIPQ	SCA	EE	-0.042	0.070*	-0.217	0.061	-
	MIPQ	OA	EE	-0.063	0.075*	-0.245	0.048	-
Indirect	MIPQ	SSS	EE	0.001	0.014*	-0.031	0.028	-
	MIPQ	HA	EE	-0.053	0.041*	-0.149	0.005	-
	MIPQ	SubA	EE	-0.023	0.031*	-0.094	0.028	-
Direct	MIPQ	-	EE	-0.034	0.092	-0.151	0.218	0.71
Total	MIPQ	-	EE	-0.146	0.077	-0.301	-0.008	0.04
	MIPQ	SCA	PA	-0.001	0.046*	-0.078	0.107	-
	MIPQ	OA	PA	0.039	0.047*	-0.039	0.151	-
Indirect	MIPQ	SSS	PA	-0.001	0.011*	-0.016	0.030	-
	MIPQ	HA	PA	-0.003	0.022*	-0.044	0.048	-
	MIPQ	SubA	PA	0.005	0.025*	-0.040	0.066	-
Direct	MIPQ	-	PA	0.201	0.066	0.074	0.342	0.003
Total	MIPQ	-	PA	0.249	0.049	0.149	0.385	<0.001

BC, bias-corrected; CI, confidence interval; SE, standard error, LLCI = Lower Limit Confidence Interval, ULCI = Upper Limit Confidence Interval. MIPQ: Mindfulness in Parenting Questionnaire, WCQ: Ways of Coping Questionnaire, SCA: Self-Confident Approach, OA: Optimistic Approach, HA: Helpless Approach, SubA: Submissive Approach, SSS: Seeking Social Support, MBI: Maslach Burnout Inventory, EE: Emotional Exhaustion, DP: Depersonalization, PA: Personal Accomplishment.
* The standard error for the indirect effect was calculated with bootstrap (5000 repetitions). Bootstrapping (with 5000 samples) was used in all mediations at a 95% CI. The mediating effect is significant when the values between the lower and upper CI contain no zeroes.Raw coefficient (b) given for total, direct and indirect effects.

The total effect of the MIPQ burnout subdimension on depersonalization was significant (b = –0.134, p = .003). When coping styles were simultaneously included in the model, the direct effect of MIPQ on depersonalization was attenuated and no longer statistically significant (b = –0.093, p = .06), indicating an indirect-only mediation pattern. HA (b = -0.045, 95% CI [-0.117, -0.033]) and SubA (b = 0.031, 95% CI [0.002, 0.073]) stress copingg styles exhibited significant mediating effects (Figure 1). Bootstrap analyses confirmed that these indirect effects were significant for HA (b= -0.045, BootSE = 0.029, 95% BCa CI [–0.117, –0.003]) and SubA (b = 0.031, BootSE = 0.018, 95% BCa CI [0.002, 0.073]) (Table 4). The model was statistically significant ($F(10, 46) = 4.65$, $p < 0.001$, $R^2 = 0.503$).

Mediation analysis showed that MIPQ exerted a significant total effect on the burnout EE subdimension(b = -0.146, p = 0.04).When coping styles were added to the model, the direct effect remained insignificant(b = -0.034, p = 0.71),but the total indirect effect was significant (BootLLCI = –0.365, BootULCI = –0.065). Examination of specific indirect effects revealed that none of the individual coping styles exhibited a statistically significant mediating effect on their own. The model was significant overall ($F(10, 46) = 2.54$, $p = 0.02$, $R^2 = 0.36$) (Table 4).

MIPQ exhibited a significant total effect on the burnout PA

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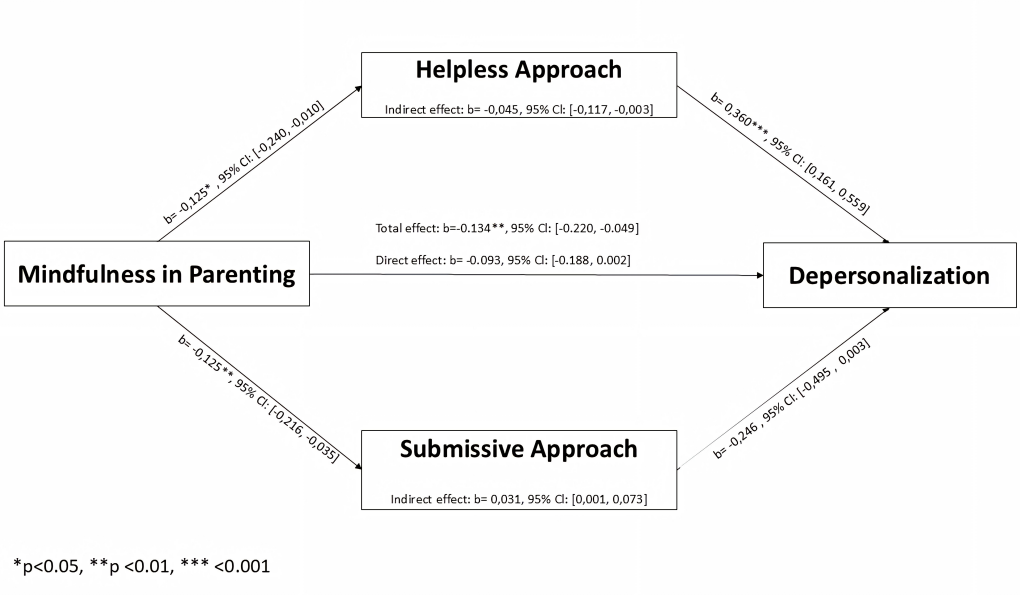

Figure 1. Direct and indirect effects of mindfulness in parenting on depersonalization.

subdimension (b = 0.249, p < 0.001). When coping styles were added to the model, the direct effect decreased but remained significant (b = 0.201, p = 0.003). The model was statistically significant overall (F(10, 46) = 3.65, p = 0.001, R^2 = 0.442). However, in the bootstrap analysis, no coping style exhibited a significant mediating effect. This shows that the effect of mindfulness in parenting on personal achievement is direct, but coping styles do not play a mediating role in this relationship (Table 4).

DISCUSSION

This study examined the relationship between mindfulness in parenting and burnout in mothers of children with ASD, and the mediating role of mothers' stress-coping styles. The findings showed significant relationships between mindfulness in parenting among mothers of children with ASD and the burnout subdimensions DP and PA, but no significant association with EE. In addition, analyses showed that HA and SubA mediated the negative effect of mindfulness in parenting on the depersonalization subdimension of burnout in parents. Styles of coping with stress did not mediate the effects of mindfulness in parenting on personal accomplishment and emotional exhaustion. The results of this study partially corroborate the first hypothesis, which states that mothers of children with ASD will experience less burnout as their mindfulness in parenting increases. They also partially support the second hypothesis that the coping styles of mothers with ASD mediate the relationship between burnout subdimensions and mindfulness in parenting. This study makes important contributions to the literature on factors affecting maternal burnout.

Research into burnout has generally focused on occupational contexts, and studies examining parental burnout that emerges alongside chronic stress specific to parenthood are scarce. Anclair et al. found that parents of children with chronic illnesses who participated in a mindfulness program saw a significant reduction in stress and burnout [11]. Pausick et al. also investigated parents in a non-clinical sample and showed that mindfulness in parenting levels predicted parental burnout [26]. Consistent with earlier studies, mothers of children with ASD in this study experienced a decrease in the depersonalization subdimension of burnout as attentive parenting increased. Mindfulness in parenting enhances parents' ability to face moments of difficulty concerning their children (such as a child crisis) in a calmer and more non-judgmental manner, rather than in an automatic and reactive one [9]. This mechanism contributes to reducing depersonalization toward the child.

One significant conclusion of the study is that stress-coping strategies, such as helplessness and submissiveness, buffered the effect of mindful parenting on depersonalization, a subdimension of burnout. Our findings show that greater mindfulness leads parents to use helpless and submissive coping styles less, and that this reduction contributes to decreased depersonalization levels. Helplessness and submissiveness are negative coping styles [20]. It has been noted that these coping mechanisms act as a moderator in the relationship between preschool instructors' burnout and mindfulness [17]. The results of another study involving a non-clinical population showed that mindfulness was significantly associated with negative, rather than positive, coping styles [8]. From this perspective, mothers of children with ASD who have low mindfulness may be more likely to adopt a negative coping style in stressful situations.

The mediation analysis in this study showed that, while mindfulness in parenting had no effect on any mediating variable with respect to the emotional exhaustion subdimension of

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burnout, it exhibited a negative total (protective) effect on emotional exhaustion. This apparent inconsistency may derive from the complexity of the mechanisms underlying this relationship. Previous research in the literature suggests that the protective effect of mindfulness-based parenting may be mediated by other psychological processes than the coping styles measured in this study [17,26,27]. Pausick et al. showed that the self-compassion and rumination type played a mediatory role in the effect of mindfulness on parental exhaustion [26]. Another study found that the association between burnout and mindfulness was mediated by perceived stress and sleep quality [27]. There is also research showing that emotional intelligence plays a mediating role in the effect of mindfulness on burnout [15,28]. In conclusion, the results of this study support the idea that mindfulness-based parenting can help mothers of children with ASD experience less emotional exhaustion, but they also point to the need for further research to better understand the fundamental psychological processes that underlie this effect.

One of the study's key conclusions is that mindfulness in the mothers of children with ASD has both a direct and a total effect on personal accomplishment, although coping styles play no mediating role. Parental self-efficacy reflects parents' awareness of themselves in the parent-child relationship [10]. Powerful maternal parental self-efficacy can reduce burnout in the mother by enhancing personal accomplishment [29]. Lippold et al. reported more positive parenting cognitions in parents with high mindfulness in parenting levels [30]. Another study reported that parental self-efficacy exerted a negative effect on parental burnout [31]. Similarly, a study of preschool teachers reported that participants with high self-efficacy exhibited lower occupational burnout [32]. Parents with high levels of mindfulness may be more likely to pause before reacting to children's behavior and to feel compassion for themselves, both of which may help them feel more competent in their roles [10]. From that perspective, the present finding shows that the effect of mindful parenting on increasing feelings of personal achievement functions directly through emotional awareness, acceptance, and non-judgmental attention processes. However, stress-coping do not contribute significantly to that relationship. Rather than altering coping strategies, mindful parenting may therefore support feelings of personal achievement by enabling parents to adopt a more accepting and non-judgmental perspective when coping with stressful situations.

From a clinical perspective, the present findings suggest that mindful parenting approaches may be meaningfully integrated into routine pediatric follow-up and family support services for children with ASD. The integration of brief mindfulness-based psychoeducational modules, emphasizing awareness, acceptance, and recognition of dysfunctional coping strategies, has the potential to assist mothers in reducing depersonalization-related burnout. Such interventions could be incorporated into multidisciplinary care models alongside behavioral and developmental approaches, thereby supporting parental well-being as part of comprehensive ASD management strategies.

This research has some limitations. Specifically, because of its cross-sectional design, the associations between variables cannot be construed as causal. Furthermore, because the data were derived from participants' self-reports, there could be a response bias. Given the number of correlation analyses conducted, no formal correction for multiple comparisons was applied. This may have increased the risk of Type I error, and the findings should therefore be interpreted with caution. Because the study was restricted to mothers with ASD in a single facility, the findings may not be widely generalizable. Finally, the assessment of gender disparities in parental burnout was not possible because fathers were omitted.

CONCLUSION

Among mothers of children with ASD, higher levels of mindfulness in parenting were associated with lower levels of parental burnout, particularly in the depersonalization dimension. The findings further suggest that helpless and submissive coping styles statistically mediate this relationship. These results contribute to understanding the psychological mechanisms linking mindful parenting to burnout in this population and highlight coping styles as an important explanatory pathway for reducing burnout.

Ethics Committee Approval: Approval for the study was granted by the Alanya Alaaddin Keykubat University Clinical Research Ethical Committee (decision no: 06-03 date: 26.03.2025).

Informed Consent: Before the study started, the participants were informed of its purpose, and their verbal and written agreement was obtained.

Peer-review: Externally peer-reviewed.

Conflict of Interest: The authors declared that they have no conflict of interest.

Author Contributions: Conception: OK, TK; Design: OK, TK; Supervision: OK, TK; Materials: OK, TK; Data collection and proccessing: OK, TK; Analysis and interpretion: OK; Literature review: OK, TK; Writing and critical review: OK, TK.

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Prognostic value of CA 19-9 elimination rate for mortality in metastatic pancreatic cancer

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MAIN POINTS

- The CA 19-9 elimination rate is a strong prognostic biomarker in metastatic pancreatic cancer.
- Patients with a high elimination rate have significantly longer overall survival.
- CA 19-9 kinetics provide more informative risk stratification than baseline CA 19-9 levels alone.
- Dynamic biomarker monitoring can complement radiologic response in treatment evaluation.

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ABSTRACT

Aim: To evaluate the prognostic value of the CA 19-9 elimination rate on survival in patients with metastatic pancreatic cancer.

Materials and Methods: This single-center retrospective cohort study included 103 adult patients with metastatic pancreatic ductal adenocarcinoma who received systemic therapy. The CA 19-9 elimination rate was calculated using baseline and 3-month values. The optimal cut-off value was determined using maximally selected rank statistics. Overall survival was analyzed using the Kaplan–Meier method and compared using the log-rank test.

Results: The mean age of the patients was 64±10.1 years, and the overall mortality rate during follow-up was 87.4%. No significant differences were observed between mortality groups with respect to demographic, clinical, or pathological characteristics (all p>0.05). The optimal cut-off value for the elimination rate (ER) was 2.33 (ER $\geq$ 2.33: high elimination; < 2.33: low elimination). Median overall survival was 25 months (95% CI: 17–31) in the high-elimination group and 8 months (95% CI: 7–14) in the low-elimination group (p = 0.043). The 12-, 36-, and 60-month survival rates were 80.4%, 18.3%, and 11% in the high-elimination group, compared with 37.6%, 2.2%, and 0% in the low-elimination group.

Conclusion: The CA 19-9 elimination rate is a significant prognostic biomarker for survival in patients with metastatic pancreatic cancer. A higher elimination rate is associated with improved short- and long-term survival outcomes, suggesting its potential utility for risk stratification and for assessing treatment response in clinical practice.

Keywords: Pancreatic cancer, CA 19-9, Elimination rate, Metastatic disease, Prognostic biomarker

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INTRODUCTION

Pancreatic cancer remains one of the most lethal malignancies worldwide and continues to pose a major challenge for healthcare systems. According to recent global cancer statistics, more than 450,000 new cases are diagnosed each year, with incidence and mortality rates showing substantial geographic variation [1,2]. The highest rates are observed in Europe and North America, whereas much lower rates are reported in Southeast Asia. These differences are largely explained by variations in demographic structure, environmental exposures, lifestyle factors, and access to diagnostic facilities [3]. Because mortality closely follows incidence, pancreatic cancer ranks among the leading causes of cancer-related death globally [1,4].

Despite ongoing progress in medical oncology, long-term survival for pancreatic cancer remains poor. Five-year survival rates are below 10%, largely because most patients are diagnosed at an advanced stage when curative treatment is no longer possible. Clinical outcome is influenced not only by disease stage but also by tumor biology, molecular features, and patient-related factors such as functional status and comorbidities [5,6]. These elements together determine treatment tolerance, response to therapy, and overall prognosis.

Carbohydrate antigen 19-9 (CA 19-9) is the most widely used serum biomarker in pancreatic cancer. Elevated CA 19-9 is detected in approximately four out of five patients, making it a useful marker for monitoring disease activity during treatment and follow-up. However, CA 19-9 lacks tumor speci-

ficity and may be increased in benign biliary disease, liver dysfunction, and other gastrointestinal malignancies, which limits its value for screening or early diagnosis [7].

For this reason, increasing attention has been directed toward the dynamic behavior of CA 19-9 rather than its absolute value at a single time point. Changes in CA 19-9 during systemic therapy may better reflect treatment response and disease activity. Several clinical studies have suggested that the pattern and speed of CA 19-9 decline after therapy initiation are more closely associated with patient outcomes than baseline levels alone.

Based on this concept, we investigated whether the CA 19-9 elimination rate, calculated using baseline and three-month measurements, could serve as a prognostic indicator of mortality in patients with metastatic pancreatic ductal adenocarcinoma.

MATERIALS AND METHODS

Study design and patients

This single-center, retrospective cohort study used the medical oncology archive and digital patient record systems at a tertiary oncology center. Patients aged 18 years or older who were diagnosed with metastatic pancreatic ductal adenocarcinoma (PDAC) and who initiated systemic therapy between 2016 and 2025 were evaluated.

This study was approved by the Göztepe Prof. Dr. Süleyman Yalçın Training and Research Hospital Non-Interventional Clinical Research Ethics Committee (date: January 8, 2026; approval no: 2026/0009).

A total of 318 patient records were screened. Based on predefined eligibility criteria, 103 patients were included in the final analysis. Sample size estimation was performed assuming a type I error of 0.05, a power of 80%, and an effect size (d) of 0.5, resulting in a minimum required sample size of 102 patients.

Inclusion criteria

Patients meeting all of the following criteria were included:

- Age: ≥18 years at diagnosis
- Diagnosis: Histopathologically confirmed pancreatic ductal adenocarcinoma
- Stage: Radiologically confirmed metastatic disease (stage IV) at diagnosis or during follow-up
- Treatment and follow-up: Receipt of at least one line of systemic therapy with available clinical follow-up data
- CA 19-9 measurements:
  - Available baseline CA 19-9 level before treatment initiation
  - At least one follow-up CA 19-9 measurement after treatment initiation
  - Measurements performed using the same laboratory or a standardized method
- Elimination rate calculability: Availability of paired CA 19-9 time-value data to allow calculation of elimination rate
- Outcome data: Known vital status with date of death or last follow-up.

Exclusion criteria

Patients were excluded if any of the following applied:

Diagnosis-related

- No histopathological confirmation of pancreatic cancer
- Neuroendocrine tumors, acinar cell carcinoma, or other rare pancreatic tumor subtypes
- Non-metastatic disease(stages I–III)

CA 19-9–related

- Absence of baseline CA 19-9 measurement
- Absence of post-treatment CA 19-9 measurement
- Insufficient or irregular CA 19-9 measurements preventing elimination rate calculation
- Known Lewis antigen–negative status with inability to produce CA 19-9 (if data available)

Biochemical or clinical conditions

- Active cholestasis, obstructive jaundice, or acute cholangitis affecting CA 19-9 levels at the time of measurement
- Presence of another concurrent malignancy likely to significantly affect CA 19-9 levels

Treatment and follow-up

- No systemic therapy received
- Missing or insufficient treatment or follow-up data
- Unknown vital status

Other

- Age <18 years
- Missing essential clinical, pathological, or laboratory data

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Table 1. Comparison of demographic and clinical characteristics according to mortality status.

Variable		Exitus (n = 90, 87.4%)	Alive (n = 13, 12.6%)	p value
Age, median (IQR)		65.0 (59.0–69.0)	68.0 (64.0–71.0)	0.261
Sex	Female	44 (48.9)	8 (61.5)	0.578
	Male	46 (51.1)	5 (38.5)	
ECOG Performance Status	0	33 (36.7)	9 (69.2)	0.169
	1	40 (44.4)	3 (23.1)	
	2	16 (17.8)	1 (7.7)	
	3	1 (1.1)	0 (0.0)	
Timing of Metastasis	De novo	71 (78.9)	10 (76.9)	1.000
	Metachronous	19 (21.1)	3 (23.1)	
Smoking	Yes	46 (51.1)	6 (46.2)	0.970
	No	44 (48.9)	7 (53.8)	
Alcohol use	Yes	16 (17.8)	2 (15.4)	1.000
	No	74 (82.2)	11 (84.6)	
Tumor location	Head	50 (56.2)	9 (69.2)	0.556
	Body–tail	39 (43.8)	4 (30.8)	
T stage	T1	4 (4.5)	2 (15.4)	0.365
	T2	29 (33.0)	4 (30.8)	
	T3	26 (29.5)	2 (15.4)	
	T4	29 (33.0)	5 (38.5)	
N stage	N0	26 (29.9)	5 (38.5)	0.336
	N1	23 (26.4)	1 (7.7)	
	N2	38 (43.7)	7 (53.8)	
Lymphovascular invasion	Present	22 (91.7)	5 (83.3)	1.000
	Absent	2 (8.3)	1 (16.7)	
Perineural invasion	Present	22 (91.7)	6 (100.0)	1.000
	Absent	2 (8.3)	0 (0.0)	
Tumor grade	Grade 1–2	19 (48.7)	6 (85.7)	0.162
	Grade 3	20 (51.3)	1 (14.3)	
Liver metastasis	Present	68 (75.6)	6 (46.2)	0.061
	Absent	22 (24.4)	7 (53.8)	
Lymph node metastasis	Regional	33 (36.7)	1 (7.7)	0.116
	Distant	29 (32.2)	6 (46.2)	
	None	28 (31.1)	6 (46.2)	
Peritoneal metastasis	Present	24 (26.7)	7 (53.8)	0.094
	Absent	66 (73.3)	6 (46.2)	
Lung metastasis	Present	15 (16.7)	3 (23.1)	0.859
	Absent	75 (83.3)	10 (76.9)	
Bone metastasis	Present	7 (7.8)	2 (15.4)	0.702
	Absent	83 (92.2)	11 (84.6)	
Treatment regimen	Folfirinox	19 (21.1)	4 (30.8)	0.153
	Gemcitabine + Nab-paclitaxel	33 (36.7)	3 (23.1)	
	5-FU based	10 (11.1)	4 (30.8)	
	Gemcitabine based	28 (31.1)	2 (15.4)	
Baseline CA 19-9, median (IQR)		547.5 (38.9–5747.2)	491.0 (160.0–2442.0)	0.846
3-month CA 19-9, median (IQR)		233.0 (21.0–3655.0)	332.0 (89.2–1601.0)	0.996
Elimination rate, median (IQR)		1.1 (0.5–3.4)	1.7 (0.5–6.5)	0.872

Abbreviations: ECOG, Eastern Cooperative Oncology Group; FU, fluorouracil; FOLFIRINOX, 5-fluorouracil + leucovorin + irinotecan + oxaliplatin; IQR, interquartile range; LVI, lymphovascular invasion; PNI, perineural invasion.

Data collection

Demographic, clinical, and pathological data; disease stage at diagnosis; metastatic sites; treatment regimens; and survival outcomes were obtained from electronic medical records and archival files. Baseline and follow-up CA 19-9 levels were recorded; efforts were made to ensure consistency in laboratory methodology. Overall survival was calculated from the date of diagnosis to the date of death or last follow-up.

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Table 2. Kaplan–Meier survival analysis.

CA 19-9 Elimination Rate	Number of Patients	Events	Mean Survival (months)	SE	Median Survival (months)	95% CI for Median (Lower–Upper)	p value
High	31.0	26	27.7	4.01	25.00	17.00-31.0	**0.043**
Low	62.0	55	12.1	1.18	8.00	7.00-14.0	

Table 3. Survival rates at 1, 3, and 5 years according to CA 19-9 elimination rate.

Elimination Rate	Time (months)	Patients at Risk	Deaths (n)	Survival (%)	Lower Limit (%)	Upper Limit (%)
High	12	23	6	80.4	67.5	95.8
High	36	5	17	18.3	8.3	40.3
High	60	2	2	11.0	3.8	31.8
Low	12	23	37	37.6	27.0	52.4
Low	36	2	17	2.2	0.3	14.9
Low	60	0	1	0.0	NaN	NaN

Calculation of CA 19-9 elimination rate

The CA 19-9 elimination rate was calculated using baseline and 3-month CA 19-9 values.

Elimination Ratio= $\frac{Baseline\ CA19-9 level - 3rd\ month\ CA19-9\ level}{Baseline\ CA19-9\ level}$

Statistical analysis

All statistical analyses were performed using JAMOVI version 2.6.17. The distributions of continuous variables were assessed using the Shapiro–Wilk test. Normally distributed variables were expressed as mean ± standard deviation, and non-normally distributed variables as median (interquartile range). Categorical variables were presented as numbers and percentages.

Comparisons between groups were performed using the Mann–Whitney U test for continuous variables and the Chi-square test or Fisher's exact test for categorical variables, as appropriate. Survival analyses were conducted using the Kaplan–Meier method, and group differences were evaluated using the log-rank test. The optimal cut-off value for the CA 19-9 elimination rate was determined using maximally selected rank statistics. A p-value < 0.05 was considered statistically significant.

RESULTS

Patient characteristics

The mean age of the study population was 64 ± 10.1 years (range: 24–84 years). During the follow-up period, 87.4% of the patients died. Of 103 patients, survival analysis based on elimination rate was performed in 93 patients due to availability of complete paired CA 19-9 measurements for cut-off classification. Baseline demographic, clinical, and pathological characteristics were compared by mortality status.

Median age did not differ significantly between patients who died during follow-up and those who remained alive (p = 0.261). Similarly, no significant differences were observed between mortality groups in sex distribution (p = 0.578), ECOG performance status, timing of metastasis (de novo vs. metachronous), smoking or alcohol use, or primary tumor location (all p>0.05). Surgical resection status was not associated with mortality (p = 0.190).

Tumor stage–related parameters, including T stage, N stage, and stage grouping, did not differ significantly between mortality groups (p = 0.365, p = 0.336, and p = 1.000, respectively). The presence of lymphovascular invasion (LVI) and perineural invasion (PNI) were also not associated with mortality (both p = 1.000). Tumor grade did not differ significantly between groups (p = 0.162).

Regarding metastatic patterns, the presence of liver, lymph node, and peritoneal metastases was not significantly associated with mortality; however, a borderline association was observed for liver metastases (p = 0.061). Lung and bone metastases were not associated with mortality (p = 0.859 and p = 0.702, respectively).

Treatment-related variables, including receipt of adjuvant chemotherapy and the type of chemotherapy regimen administered, were not significantly associated with mortality (all p>0.05). Baseline and 3-month CA 19-9 levels, the absolute change in CA 19-9, and the CA 19-9 elimination rate also did not differ significantly between mortality groups (all p>0.05) (Table 1).

Determination of the optimal cut-off for CA 19-9 elimination rate

Figure 1 shows the distribution of CA 19-9 elimination rate values and the results of maximally selected rank statistics. Lower elimination-rate values occurred more frequently, whereas higher values spanned a wider range.

Using maximally selected rank statistics, the optimal cut-off value for the CA 19-9 elimination rate was determined to be 2.33; at this value, the standardized log-rank statistic reached its maximum, indicating the greatest separation in survival between groups. Patients with an elimination rate ≤2.33 were classified as having a low elimination rate, whereas those with values >2.33 were classified as having a high elimination rate.

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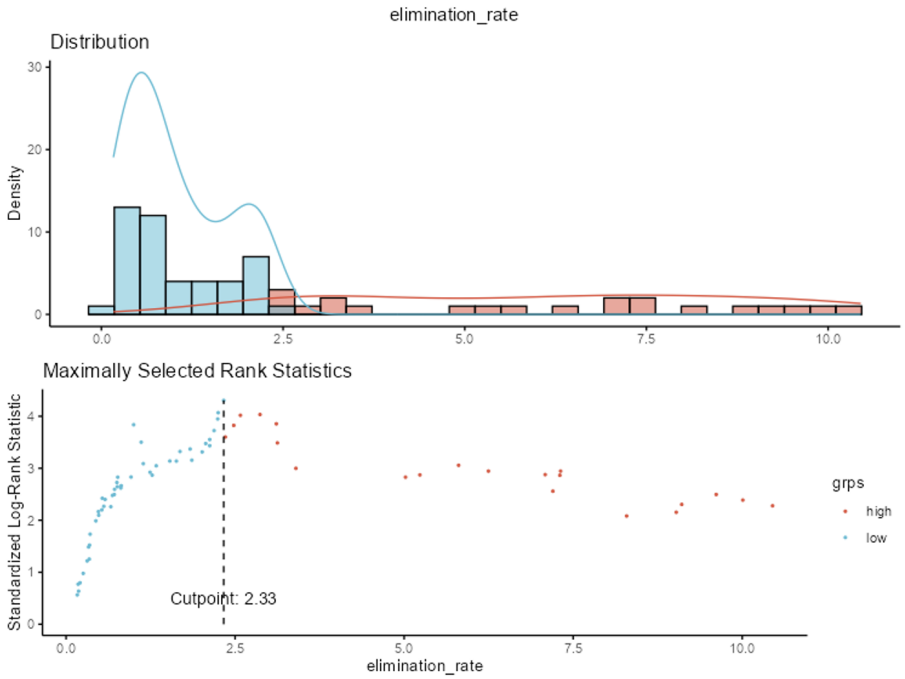

Figure 1. Elimination rate (according to cut-off group).

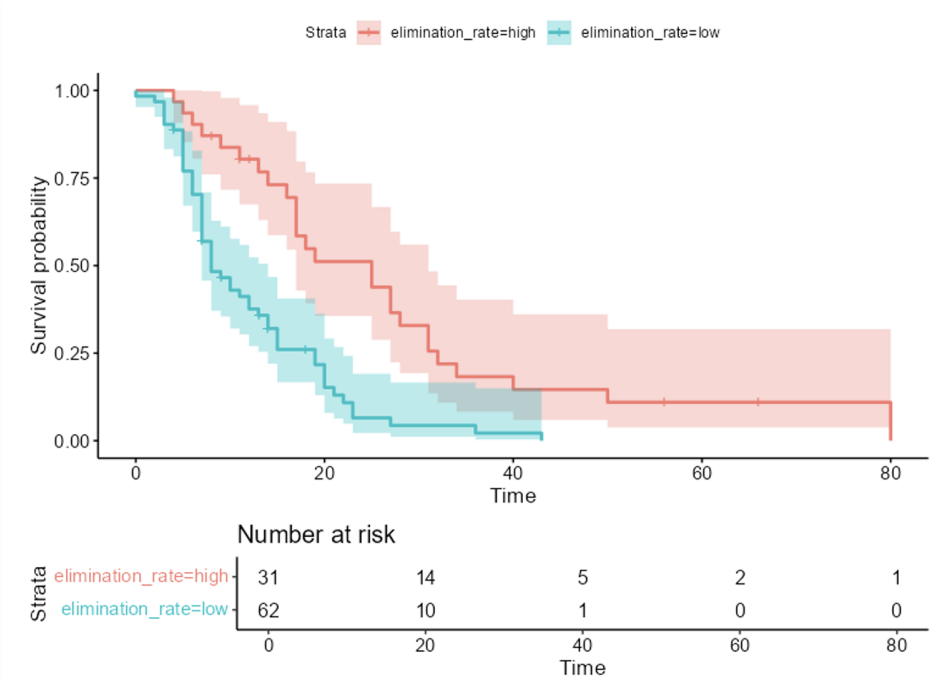

Figure 2. Survival according to elimination rate.

Survival according to CA 19-9 elimination rate

Median overall survival in the high-elimination group was 25 months (95% CI: 17–31), compared with 8 months (95% CI: 7–14) in the low-elimination group (p = 0.043) (Table 2, Figure 2).

Patients with a high CA 19-9 elimination rate had a substantially lower risk of death during follow-up compared with those with a low elimination rate.

Long-term survival outcomes

In the high-elimination group, the 12-, 36-, and 60-month survival rates were 80.4%, 18.3%, and 11.0%, respectively. In contrast, in the low-elimination group, the corresponding survival rates were 37.6%, 2.2%, and 0%, respectively (Table 3).

These findings demonstrate a marked and persistent survival advantage in patients with a high CA 19-9 elimination rate across short-, intermediate-, and long-term follow-up periods.

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DISCUSSION

CA 19-9 is the most widely used biomarker in pancreatic cancer and plays an important role in routine clinical monitoring. Numerous studies have established its diagnostic and prognostic relevance, as well as its usefulness for evaluating response to treatment [8].In addition to reflecting tumor burden, CA 19-9 has also been shown to correlate with surgical resectability, pathological stage, and likelihood of achieving complete tumor removal [9].

In this study, we demonstrated that the rate of decline in CA 19-9 after initiation of systemic therapy has a strong association with survival in patients with metastatic pancreatic ductal adenocarcinoma. Patients with a high CA 19-9 elimination rate experienced significantly longer overall survival and markedly better long-term survival rates compared with those with low CA 19-9 elimination rate. These findings indicate that CA 19-9 kinetics provide clinically meaningful prognostic information beyond baseline measurements.

Previous investigations have highlighted the importance of CA 19-9 dynamics. In a prospective study of locally advanced pancreatic cancer, Vainshtein and colleagues showed that both baseline CA 19-9 level and increases during chemoradiotherapy were independent predictors of progression-free and overall survival [10]. Notably, changes in CA 19-9 were more closely associated with outcome than radiologic progression, suggesting that biochemical markers may capture biologic tumor activity that is not fully reflected by imaging.

Similarly, Yoo et al. demonstrated that combining contrast-enhanced computed tomography (CT), ^{18}F-FDG Positron emission tomography (PET)/MRI, and CA 19-9 improved the prediction of treatment response and resectability in patients receiving neoadjuvant therapy [11].These data support the concept that serum biomarkers and advanced imaging modalities provide complementary information, particularly in pancreatic cancer, where fibrosis and desmoplastic reaction can obscure viable tumor tissue on conventional CT.

Our results are consistent with these observations, but extend them to metastatic disease by applying a quantitative kinetic parameter, rather than static CA 19-9 values. Instead of categorizing patients simply as responders or non-responders, clinicians can use the elimination rate to continuously stratify tumor behavior and prognosis.

The clinical importance of integrating CA 19-9 with radiologic findings was clearly demonstrated by Kim et al. In patients treated with first-line FOLFIRINOX, radiologic response based on RECIST criteria alone was insufficient to distinguish survival between patients with partial response and stable disease [12]. When CA 19-9 response was added, survival differences became evident, with the best outcomes observed in patients who achieved both disease control on imaging and biochemical normalization. This finding highlights a key limitation of morphology-based imaging and emphasizes the value of biochemical monitoring.

Our data further refine this approach by showing that the rate of CA 19-9 decline has important prognostic significance. Patients with rapid biomarker elimination had substantially longer survival, suggesting that CA 19-9 kinetics may reflect underlying tumor sensitivity to chemotherapy and biological aggressiveness more accurately than absolute values.

Accurate assessment of disease extent remains challenging in pancreatic cancer, as micrometastatic spread and true tumor burden are often underestimated by imaging alone [12]. In this setting, biomarkers that capture systemic tumor activity become particularly valuable. In resectable pancreatic cancer, Jeong et al. reported that a preoperative risk model incorporating CA 19-9, CT, and ^{18}F-FDG PET/CT predicted recurrence-free survival with accuracy comparable to pathological staging [13]. Likewise, Zhong et al. developed nomograms combining CT features and CA 19-9 to estimate progression-free survival in locally advanced disease [14]. However, these models relied on static CA 19-9 measurements, whereas our findings indicate that dynamic CA 19-9 elimination provides additional prognostic information in metastatic disease.

Early combined assessment of CA 19-9 and imaging has also been shown to improve prediction of outcomes. Kim et al. demonstrated that CT together with CA 19-9 response at eight weeks was superior to RECIST criteria alone for predicting survival in non-metastatic pancreatic cancer [15] Our study builds on this concept by demonstrating that continuous biomarker kinetics remain prognostically informative even in advanced-stage disease.

Current NCCN guidelines recommend interpretation of CA 19-9 in conjunction with imaging when assessing treatment response in pancreatic cancer [16]. Our results support this recommendation and suggest that incorporating the CA 19-9 elimination rate into routine follow-up may improve early risk stratification and help guide treatment decisions for patients with metastatic pancreatic cancer.

Limitations

This study has several limitations. First, its single-center design and the cohort's high mortality rate may introduce selection bias. Second, the retrospective nature of the study and reliance on medical records may result in information bias due to missing or incomplete data. In addition, variations in the timing of CA 19-9 measurements and in treatment regimens may have influenced biomarker dynamics. Another limitation of this study is the absence of multivariable Cox regression analysis. Due to the retrospective design and the limited sample size, adjustment for potential confounders was not performed. Therefore, the findings should be interpreted as demonstrating an association rather than independence.

However, a major strength of this study is the evaluation of CA 19-9 using a dynamic kinetic parameter, the elimination rate, rather than relying solely on static absolute values. This

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approach provides a more nuanced assessment of treatment response and tumor behavior and constitutes a novel contribution compared with most previous studies.

CONCLUSION

In conclusion, dynamic changes in CA 19-9 after initiation of systemic therapy are a significant prognostic factor for mortality in patients with metastatic pancreatic cancer. A higher CA 19-9 elimination rate is associated with superior short-, intermediate-, and long-term survival outcomes. These findings suggest that the CA 19-9 elimination rate may serve as a useful complementary tool for risk stratification and treatment response monitoring in clinical practice. Prospective studies integrating CA 19-9 kinetics with imaging-based parameters are warranted to further refine individualized treatment strategies in pancreatic cancer.

Ethics Committee Approval: This study was approved by the Göztepe Prof. Dr. Süleyman Yalçın Training and Research Hospital Non-Interventional Clinical Research Ethics Committee (date: January 8, 2026; approval no: 2026/0009).

Informed Consent: Written informed consent was waived due to the retrospective design of the study and the use of anonymized data.

Peer-review: Externally peer-reviewed.

Conflict of Interest: The authors declare that they have no conflict of interest.

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