

Descriptive Temporal and Seasonal Distribution in Peptic Ulcer Perforation: A Ten-Year Cohort Study

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ABSTRACT

Introduction: Peptic ulcer perforation (PUP) is a critical condition in which gastric or duodenal ulcers rupture, leading to leakage of abdominal contents and life-threatening complications. While factors such as age, gender, smoking, and medication use are associated with PUP, a significant question remains unanswered: why does PUP often occur in patients without prior symptoms of peptic ulcer disease? Seasonal patterns, which may act as external triggers, have been underexplored in this context. This study aims to descriptively examine the monthly and seasonal distribution of PUP incidence over a ten-year period to better understand its occurrence and potential environmental influences.

Methods: A retrospective cohort study was conducted at a Turkish tertiary hospital, gathering data on PUP cases from January 1, 2010, to December 31, 2019. To ensure a focused cohort, we excluded patients with prior gastric surgery and included only confirmed operative cases. We collected demographic (age and gender) and clinical (perforation site and seasonal trends) data. Descriptive statistics and appropriate non-parametric tests (Kruskal-Wallis) were used to analyze patient characteristics across seasons. The study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for reporting observational studies.

Results: Among 287 PUP patients, who were predominantly male (83.3%) with a mean age of 42.8 years, a significant seasonal imbalance was noted. PUP cases were most frequent in summer (June to August) (34.1%) and least frequent in winter (20.6%) ($p=0.012$). July recorded the highest number of PUP incidents, while September recorded the fewest PUP incidents. The median age also varied significantly across seasons ($p=0.034$), with the youngest patients observed in autumn.

Conclusion: This descriptive study found a significant seasonal imbalance in PUP case occurrence, with higher case frequency in summer and lower-case frequency in autumn and winter. These findings serve as descriptive evidence of PUP patterns in this cohort and warranting further analytical research into potential underlying mechanisms.

Keywords: Seasonal distribution, peptic ulcer disease, perforation, incidence

Introduction

Peptic ulcer disease (PUD) is a common gastrointestinal disorder characterized by ulcers in the stomach or duodenum lining. Despite effective modern treatments, PUD poses health risks due to complications such as bleeding and perforation (1). While the overall prevalence of PUD has declined in recent decades due to improved management strategies, complications such as peptic ulcer perforation (PUP) remain significant clinical concerns. PUP is a life-threatening emergency that occurs when an ulcer erodes through the stomach or duodenal wall and requires immediate intervention, as it can lead to peritonitis and sepsis if untreated (2,3).

Despite advancements in medical management, including the use of proton pump inhibitors and eradication therapies for *Helicobacter pylori* (*H. pylori*), the incidence of PUP remains significant (4). As with PUD, several risk factors for PUP have been identified, including older age, male gender, smoking, non-steroidal anti-inflammatory drug (NSAID) use, and *H. pylori* infection. However, growing evidence indicates that external factors, such as seasonal variations, may also influence PUP incidence, which is the primary focus of this study.

Seasonal patterns in gastrointestinal conditions, including PUD and its complications, have been the subject of ongoing research, particularly in regions with pronounced seasonality. Seasonal variation in peptic ulcer-



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related conditions has been examined in several studies, with some reporting increased ulcer symptoms and complications in colder months, possibly owing to lifestyle changes, dietary factors and environmental stressors (5,6). While studies have examined PUD seasonality, fewer have focused specifically on PUP, and the results have been inconsistent. For example, some studies have found higher PUP rates in winter, hypothesizing that stress, medication use, or an increased incidence of respiratory infections during cold weather might exacerbate ulceration (6). Conversely, research, including the findings of the present study, has suggested an increased incidence of PUP during the summer months, possibly due to dehydration or increased outdoor activity (7).

The implications of these findings extend beyond academic interest. Recognizing seasonal patterns in the presentation of PUP cases can inform the strategic allocation of surgical and critical care resources. However, the mechanisms underlying PUP, which often occurs in patients without prior symptoms of PUD, remain poorly understood. This phenomenon raises critical questions about the role of external triggers, such as seasonal and environmental factors, in initiating a perforation in otherwise asymptomatic individuals. In this study, we aim to address these gaps by describing the seasonal distribution of PUP incidence, providing insights into potential temporal patterns, and offering preliminary evidence-based recommendations for its prevention and management. Specifically, the primary research question of this study is: What are the monthly and seasonal distributions of PUP cases over a ten-year period in a Turkish tertiary-care center cohort?

Methods

Study Design and Setting

This retrospective cohort study was conducted at the University of Health Sciences Türkiye, Ümraniye Training and Research Hospital, a tertiary care center in Türkiye. The study aimed to investigate the seasonal distribution of patients undergoing surgery for PUP between January 1, 2010, and December 31, 2019. Ethical approval for the study was obtained from the Ethics Committee of the University of Health Sciences Türkiye, Ümraniye Training and Research Hospital (approval number: 2024/288, date: 05.09.2024). This study adhered to the principles of the Declaration of Helsinki and its amendments, and patient data were anonymized before analysis. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for cohort studies.

Patient Selection and Exclusion Criteria

The retrospective study included all patients diagnosed with PUP during the specified time period. Specifically, patients were included only if they underwent an emergency surgical procedure (laparoscopy or laparotomy) during which a PUP was visually confirmed. To ensure a homogeneous study population, patients with a history of gastric surgery, which could influence the risk of perforation, were excluded from the study. This exclusion was necessary to limit confounding factors, as prior gastric surgeries might alter the natural course of ulcer disease and affect the likelihood of perforation. All patients included in

the study underwent emergency surgery for confirmed PUP. Patients in whom a perforation was not confirmed during diagnostic laparoscopy or laparotomy were excluded. As this study is descriptive, a control group of patients with non-perforated PUD was not included. Clarifying the exclusion criteria, we excluded:

- Patients with a history of any prior gastric or upper gastrointestinal surgery.
- Patients where PUP was not confirmed intraoperatively.

Data Collection

Data were retrospectively collected from hospital registries, medical records, and surgical reports. Demographic variables, including age and gender, were obtained, along with clinical information about the site of perforation (gastric or duodenal) and the date of diagnosis or surgery. Given that seasonal patterns were a focus of the study, seasons were categorized as follows: spring (March, April, May), summer (June, July, August), autumn (September, October, November), and winter (December, January, February). This definition of the seasons aligns with the established meteorological categorization for Türkiye. The site of perforation (gastric or duodenal) was also recorded for each patient.

Statistical Analysis

Statistical analysis was conducted using SPSS Statistics 22.0 (SPSS Inc., Chicago, IL). Descriptive statistics were used to summarize demographic and clinical characteristics. Continuous variables, such as age, were presented as mean \pm standard deviation or median [interquartile range (IQR)] depending on the data distribution. Either chi-square test or Fisher's exact test was applied to categorical variables (e.g., gender and season) to assess seasonal differences in case proportions.

To compare age (a continuous variable) across the four seasonal categories, the Kruskal-Wallis one-way analysis of variance by ranks test was used because a preliminary Shapiro-Wilk test indicated that age was not normally distributed across the seasonal groups. The Kruskal-Wallis test was chosen as the appropriate non-parametric method for comparing medians across three or more independent groups. Poisson regression was used to estimate the relative risk of PUP occurrence in each season relative to the least frequent season (winter), providing further insight into the temporal imbalance in case distribution. Poisson regression was selected because of its suitability for modeling count data (the number of perforations) and comparing incidence rates over time.

All statistical tests were two-sided, and a p-value of ≤ 0.05 were considered statistically significant. Confidence intervals (CI) were calculated where applicable, and results were presented with 95% CI. Given limitations in the available data, no additional adjustments were made for potential confounders such as NSAID use, *H. pylori* infection, or smoking, because these variables were not systematically recorded for all patients. However, their potential impact on PUP incidence is acknowledged in the Discussion section.

Results

Demographic Characteristics

A total of 287 patients diagnosed with PUP were included in the study. Of these, 83.3% were male and 16.7% were female. The mean age of the overall cohort was 42.8 ± 18.2 years (95% CI: 39.0-43.3), with an age range from 18 to 93 years. The median age was 41.0 years (IQR: 28.0-55.0). The gender distribution remained consistent across seasons, but the male-to-female ratio was highest during autumn (8.9:1) and lowest during spring (2.9:1). The distribution of perforation sites revealed that 210 patients (73.2%) had duodenal perforations, and 77 patients (26.8%) had gastric perforations. The seasonal distribution of gastric and duodenal perforations did not differ significantly ($p=0.234$).

Seasonal Distribution

Seasonal analysis revealed a significant imbalance in PUP case counts, with the highest number of cases occurring in summer (34.1%), followed by spring (24%), autumn (21.3%), and winter (20.6%) (chi-square test, $p=0.012$). The peak in PUP incidence was observed in July, while the lowest number of cases occurred in September. This seasonal imbalance is clearly visualized in Figure 1, with detailed monthly fluctuations presented in Figure 2. Gender-specific analysis indicated a higher PUP incidence among males across all seasons, although no statistically

significant gender difference in incidence was observed between seasons ($p=0.119$). Detailed demographic comparisons and patient characteristics by season are summarized in Table 1.

Age Comparison and Poisson Regression Analysis

The Kruskal-Wallis test indicated a statistically significant difference in the median age of patients across the four seasonal groups ($p=0.034$).

Specifically, patients diagnosed with PUP in autumn were significantly younger (mean age 36.6 ± 15.4 years; median 34.0 years) than those diagnosed in other seasons.

Poisson regression analysis demonstrated a significantly higher incidence of PUP during the summer months (June-August) ($p=0.019$) compared to other seasons. Regression statistics by season are shown in Table 2.

Seasonal and Monthly Fluctuations

Notably, July consistently showed the highest monthly incidence of PUP, aligning with the overall summer peak observed in the seasonal analysis. The regression analysis results, highlighting the seasonal distribution of cases in PUP incidence, are summarized in Table 2.

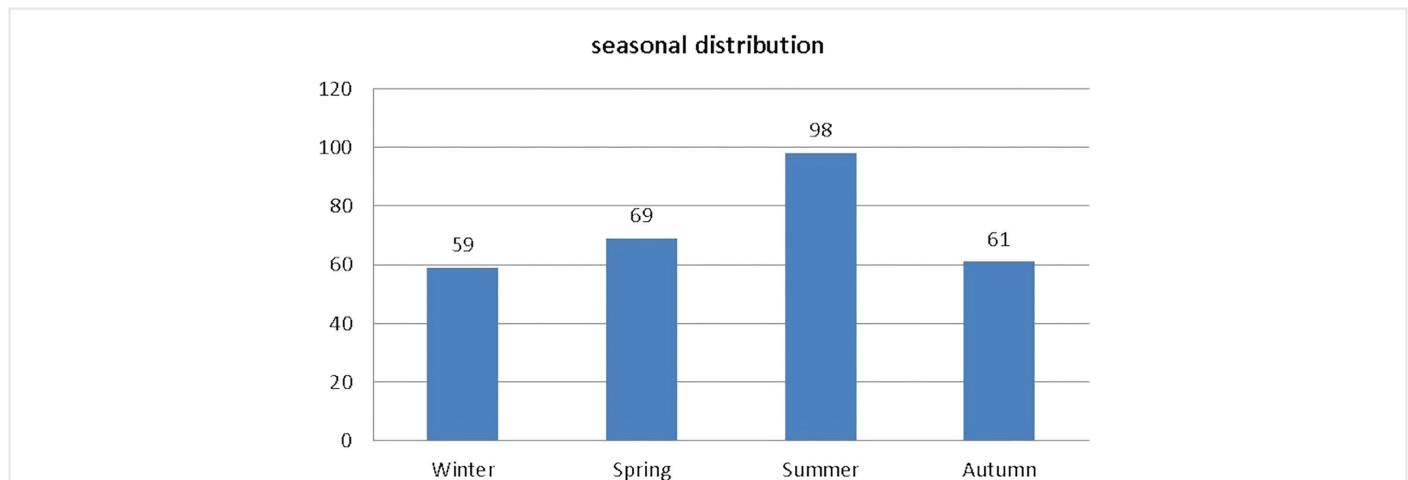


Figure 1. Seasonal distribution in patients with peptic ulcer perforation

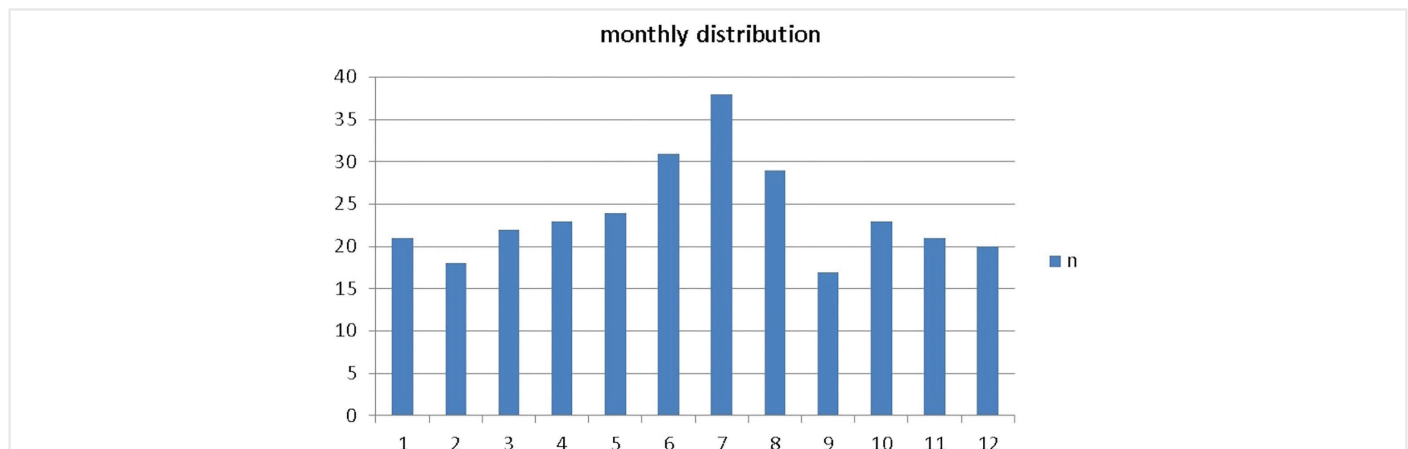


Figure 2. Monthly distribution in patients with peptic ulcer perforation

Table 1. Characteristics of patients according to seasons

n (%)	Total	Winter	Spring	Summer	Autumn	p value
	287	59 (20.6)	69 (24)	98 (34.1)	61 (21.3)	0.012*
Gender; male n (%)	239 (83.3)	50 (20.9)	51 (21.3)	85 (35.6)	53 (22.2)	0.119
Female n (%)	48 (16.7)	9 (18.8)	18 (37.5)	13 (27.1)	8 (16.7)	
Age Mean (IQR)	41.0 (28.0-55.0)	45.0 (30.0-62.0)	43.0 (27.0-57.0)	43.0 (28.0-58.0)	34.0 (25.0-48.0)	0.034*
95% CI for mean LB-UB	39.0-43.3	40.3-51.6	38.7-47.9	36.6-43.3	32.2-40.5	
Min-max	18-93	18-93	19-82	18-89	18-87	

*p<0.05 was considered statistically significant. Age comparison test: Kruskal-Wallis. p<0.05 was considered statistically significant. IQR: Interquartile range, CI: Confidence interval, Min: Minimum, Max: Maximum, LB: lower bound, UB: upper bound

Table 2. Poisson regression statistics by season

	Coefficients	Standard error	t-value	p value	Lower-upper 95 %
Intercept	6.301	1.364	4.621	0.000	3.520-9.082
Time-period	-0.018	0.051	-0.347	0.731	-0.122-0.086
Spring	0.462	1.490	0.310	0.758	-2.576-3.501
Summer	3.702	1.492	2.481	0.019*	0.658-6.746
Autumn	0.498	1.497	0.332	0.742	-2.555-3.550

*p<0.05 was considered statistically significant

Discussion

PUP is a serious complication of PUD, and its seasonal occurrence has been the focus of several studies. While previous research on this topic has yielded valuable insights, many studies have been limited by small sample sizes or inconsistent results due to geographical and climatic differences (8,9). Our study, based on ten years of data from a tertiary care center in Türkiye, provides a more comprehensive descriptive analysis of PUP case incidence and its seasonal fluctuations. Our findings indicate a significant seasonal imbalance in the distribution of PUP cases, with the highest incidence in summer and the lowest in winter. Notably, the peak incidence in July and the trough in September offer valuable insights into the temporal patterns of these diseases.

Seasonal variation in gastrointestinal diseases, including PUD and PUP, has been extensively reported. Some studies have suggested that colder months are associated with a higher incidence of PUD, possibly due to increased stress, dietary changes, or the exacerbation of chronic conditions (5-7). However, our findings indicate a different seasonal pattern for PUP, with a marked increase during the summer months, particularly in July. This is consistent with findings of Liu et al. (9), who observed similar trends in China, where warmer temperatures were associated with an increased incidence of PUP. This divergence between PUD and PUP serves as descriptive evidence that seasonal factors may be temporally associated with ulcer perforation, independently of PUD symptomatology. The question of why PUP often occurs in asymptomatic patients remains unanswered, and our study aimed to explore whether seasonal patterns might provide insights into these cases.

The temporal relationship driving the seasonal variation in PUP is likely multifactorial. One plausible explanation is that dietary habits during the summer months may play a significant role. Increased consumption of spicy, fatty, and acidic foods during the summer, combined with

higher use of alcohol and tobacco, could exacerbate gastric irritation and increase the risk of ulcer perforation. Studies have shown that certain dietary factors, such as fatty foods, can stimulate gastric acid production, leading to mucosal damage and increased susceptibility to ulceration (10). This hypothesis aligns with our observation of a higher incidence of PUP during summer, a period traditionally associated with more frequent outdoor social gatherings, increased alcohol consumption, and greater intake of rich foods. Additionally, regional dietary habits in Türkiye during the summer months often include increased consumption of grilled meats, spicy salads, and cold, acidic beverages, which may contribute to gastric irritation.

In contrast, colder months are often linked to a higher incidence of PUD symptoms, particularly among individuals with chronic ulcer disease (6,7). However, the progression of peptic ulcer to perforation may be influenced by various factors, as reflected by the lower incidence of PUP in winter in our study. Some studies have postulated that colder temperatures may reduce gastrointestinal motility and slow gastric emptying, potentially worsening ulcer symptoms without necessarily increasing the risk of perforation (11,12). Our study supports the descriptive finding that PUP presentations are less frequent in winter, highlighting a temporal pattern that may be distinct from non-complicated PUD.

The influence of environmental factors, such as temperature and humidity, has also been proposed to contribute to the seasonal variation in PUP (9). Warmer temperatures, such as those experienced during summer in Türkiye, may be associated with dehydration and alterations in blood flow, which could reduce the protective mucus layer in the gastrointestinal tract, thereby increasing the risk of ulcer perforation. Previous studies have suggested that the incidence of ulcers, particularly duodenal ulcers, may be inversely correlated with

temperature, with lower temperatures associated with increased ulcer activity (11). However, the lack of region-specific atmospheric data in our study limits the ability to perform a comprehensive analytical correlation between climatic variations and PUP incidence. Future studies integrating detailed meteorological data are essential to establish these associations more conclusively.

The most notable finding regarding patient characteristics was the significantly younger median age (34.0 years) observed in patients presenting with PUP during the autumn months ($p=0.034$), a difference that warrants discussion. Although speculative given the descriptive nature of our data, this observation may suggest that a different set of factors drives perforation in younger individuals during this season. For instance, younger patients are generally less likely to have chronic *H. pylori*-driven ulcers and may have perforations that are acutely triggered by lifestyle factors. The transition from the high-stress, dietary-excess summer vacation period to the onset of the academic or work year in autumn, with September having the lowest overall incidence, may be associated with delayed presentations of ulcers or acute stress-related perforations in a younger, more reactive demographic. Alternatively, this may reflect a temporary shift in the use of NSAIDs among younger, physically active individuals as seasonal sports or activities begin. This distinct age-related pattern observed during autumn highlights the need for future analytical studies to examine the interplay of age, lifestyle, and acute triggers in PUP.

Another important factor that may contribute to seasonal patterns in PUP is the prevalence of *H. pylori* infection. Although *H. pylori* is a well-established cause of PUD, the seasonal patterns of this infection are less well understood (13). Some studies have suggested that *H. pylori* infection rates may fluctuate seasonally, with higher rates during warmer months, potentially contributing to increased PUP in summer (14). However, our study did not include data on *H. pylori* status, and further research is needed to clarify, either descriptively or analytically, the role of this infection in the seasonal distribution of PUP cases.

Additionally, the role of NSAID use in the incidence of PUP should not be overlooked. NSAIDs are known to impair the gastric mucosal defense mechanisms, making the gastrointestinal tract more vulnerable to injury. Studies have demonstrated circadian rhythms in gastrointestinal tolerance to NSAIDs, with greater susceptibility to damage occurring in the morning compared to nighttime administration (15). However, our study did not collect data on NSAID use among the study population, which constitutes a limitation to be addressed in future analytical studies.

The observed summer peak in PUP in our study is consistent with findings from other studies reporting seasonal variations in gastrointestinal conditions, particularly in warmer climates. Several factors may explain the higher incidence of PUP during the summer, including increased consumption of spicy and acidic foods, greater alcohol intake, and heightened use of NSAIDs for pain management during periods of increased outdoor activity (13). Stress levels during summer vacations and travel, coupled with disrupted dietary patterns, may temporarily exacerbate existing gastric conditions or be associated with the progression from asymptomatic ulcers to perforation. Importantly, the

occurrence of PUP among non-symptomatic PUD patients suggests that acute external factors, such as those prevalent in summer months, may act as direct triggers rather than resulting from a gradual progression of ulcer severity. However, our study did not include data on these specific lifestyle factors, which limits the inferences we can draw regarding their impact on PUP incidence. Further research incorporating these variables is needed to strengthen this hypothesis.

The lower incidence of PUP observed in winter and autumn, particularly in September, could reflect changes in dietary habits and reduced NSAID use as outdoor activities decrease and stress levels potentially normalize after the summer vacation. Previous studies have suggested that lower stress and more regular dietary habits during winter months may contribute to a reduced risk of ulcer complications (16). Additionally, colder months may lack the acute triggering factors, such as dehydration or dietary excess, that are more prevalent in summer. This raises questions about the role of environmental conditions not only in ulcer formation but also in the sudden transition from ulceration to perforation. Nonetheless, these conclusions remain speculative in the absence of direct data on patient stress levels, medication use, and diet among our study population.

Additionally, our analysis did not account for variations in *H. pylori* infection rates, which could play a significant role in ulcer disease seasonality (13,14). While chronic *H. pylori* infection is well-known to contribute to PUD, the interaction between infection prevalence and acute seasonal triggers in PUP remains unclear. Higher infection rates during summer could amplify mucosal vulnerability caused by external factors, increasing the risk of perforation. Future studies should investigate the interplay between *H. pylori* status and seasonal triggers to better understand this relationship. Fluctuations in atmospheric temperature and humidity are another factor worth exploring, as several studies indicate that warmer temperatures and higher humidity may weaken gastric mucosal defenses (9,17,18). However, our study did not include region-specific meteorological data, which is a notable limitation. Future studies should incorporate detailed environmental data to better understand the climatic influences on PUP.

Implications for Clinical Practice

Recognizing the seasonal imbalance in PUP incidence has important clinical implications. Healthcare systems, especially in regions with clear seasonal variations, can anticipate higher demands for surgical interventions and acute care during the summer months. Hospitals could benefit from strategic planning, ensuring the availability of resources and personnel during periods of increased incidence. Furthermore, public health campaigns during high-risk months, particularly in summer, can focus on reducing risky behaviors such as excessive NSAID use and consumption of irritating foods, and on promoting adherence to ulcer prevention guidelines (16,19). By incorporating education about the potential for silent progression of ulcers to perforation, clinicians can empower patients to seek timely medical attention even in the absence of traditional ulcer symptoms. Educating patients about the signs of peptic ulcers and encouraging early medical intervention during high-incidence periods could reduce the risk of complications, such as perforation, and ultimately improve patient outcomes.

Given the high mortality associated with PUP, which is well-documented in surgical literature, it is imperative to emphasize the importance of early diagnosis and intervention. While we did not specifically report mortality rates in this study because of its retrospective design and focus on seasonal patterns, we acknowledge that mortality is a significant concern in PUP cases.

Exploration of Additional Factors

Although this study highlights seasonal patterns in PUP, it is important to acknowledge the influence of other critical factors, such as dietary habits, stress, medication use, and *H. pylori* infection rates, which also fluctuate seasonally and can affect PUP incidence (13). In asymptomatic cases of PUD, these external factors may act as acute triggers, leading directly to perforation without warning signs. This phenomenon underscores the need for a deeper exploration of the mechanisms underlying the transition of ulcers from dormancy to perforation in response to seasonal influences. For example, studies have shown a correlation between seasonal infections and increased ulcer activity: gastrointestinal infections are often more prevalent in warmer months, which may increase the risk of ulcer perforation (14). Including data on *H. pylori* infection (a major cause of peptic ulcers) in future studies would provide valuable insights into the interaction between infection rates and PUP incidence (13,20,21). Furthermore, while natural disasters (e.g., earthquakes) and conflicts can significantly impact healthcare systems and patient stress levels, there were no major events of this nature during the study period that would have directly influenced the observed seasonal trends in our center.

Study Limitations

Our study has several limitations inherent in its design and data collection.

First, the descriptive and retrospective nature of this single-center cohort means that we can report only the temporal distribution of PUP cases. Without a control group of non-perforated PUD patients or a population-based reference, we cannot establish causality and can only provide evidence that a seasonal pattern exists.

Second, a major limitation is the lack of detailed data on key confounding factors, including NSAID use, (*H. pylori* infection status, smoking, and alcohol consumption. Since these are primary determinants of ulcer disease, their absence prevents a deeper analytical exploration of the mechanisms driving the observed seasonal pattern, particularly why perforations occur in asymptomatic patients.

Third, we did not include detailed meteorological data on local temperature, humidity, or atmospheric pressure. This limits our ability to correlate climatic variations with the observed seasonal changes in PUP incidence (9).

Fourth, while the study spanned ten years, we did not analyze year-by-year trends, which could have revealed whether the seasonal pattern persisted or shifted over time due to changes in clinical practice or environmental factors.

Finally, the single-center design and the relatively small sample size in some seasonal subgroups may limit the generalizability and statistical

power of our findings to other populations or geographic regions with different climatic conditions. We acknowledge that our focus on surgical cases precludes reporting the full incidence of non-perforated peptic ulcers or bleeding from peptic ulcers in the general population; this omission avoids potential selection bias that would result from reporting unverified data.

Future Directions for Research

Future research should aim to address these limitations by including larger, multi-center studies that capture a broader population base and more diverse climatic conditions.

Crucially, future analytical studies must include a control group of patients with non-perforated PUD or use population-based incidence rates to distinguish overall changes in ulcer incidence from specific seasonal factors precipitating perforation.

Furthermore, integrating specific, prospectively collected data on *H. pylori* infection rates, NSAID use, dietary habits, and stress levels would provide a more comprehensive understanding of the factors influencing PUP (20,21). Detailed meteorological data should also be collected and correlated with case counts to examine the impact of environmental variables.

Moreover, analyses of annual trends could reveal how seasonal patterns are influenced by advances in medical therapies, changing environmental exposures, and shifting lifestyle behaviors. This would clarify whether the mechanisms driving seasonal PUP incidence are static or dynamic. Finally, studies examining the occurrence of PUP among non-symptomatic PUD patients could provide valuable insights into acute external triggers that bypass the usual progression of ulcer symptoms. Further studies should investigate the relationship between uncomplicated peptic ulcers and perforation rate to better understand disease progression.

Conclusion

Our descriptive study underscores the temporal imbalance in the presentation of PUP, with a clear increase in incidence during the summer months and a lower incidence in autumn and winter.

This pattern highlights the need for public health initiatives that promote healthier lifestyle choices, including reduced NSAID use and adherence to dietary recommendations during high-risk periods such as summer. Increasing physicians' awareness of these seasonal trends in PUP can improve preparedness and patient management, particularly with respect to the significantly younger patient demographic identified in autumn.

By anticipating higher PUP incidence during summer and preparing accordingly, healthcare systems can better manage patient care and potentially reduce morbidity and mortality associated with peptic ulcers.

Ethics

Ethics Committee Approval: Ethical approval for the study was obtained from the Ethics Committee of the University of Health Sciences Türkiye, Ümraniye Training and Research Hospital (approval number: 2024/288, date: 05.09.2024).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions: Surgical and Medical Practices - İ.K., F.B., H.T., O.E.; Concept - İ.K., F.B., H.T., O.E.; Design - T.C., H.K.T., K.T.; Data Collection or Processing - İ.K., F.B., H.T., O.E.; Analysis or Interpretation A.A., T.C., H.K.T., K.T.; Literature Search - A.A., T.C., H.K.T., K.T.; Writing - İ.K., F.B., H.T., O.E., A.A., T.C., H.K.T., K.T.

Conflict of Interest: No conflict of interest was declared by the authors.

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