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Research Article

The impact of perception and fear on the adoption of protective measures against covid-19: A mediation analysis

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Abstract

Objective: COVID-19 has had physical, mental, and social impacts worldwide, yet uptake of protective behaviors varied. We aimed to assess how COVID-19 disease perception and fear relate to adoption of precautions among adults in Türkiye.

Methods: After ethics approval, we conducted a cross-sectional online survey in Türkiye (March 1–April 1, 2021) using researcher networks for recruitment. Measures included the COVID-19 Disease Perception Scale (dangerousness and contagiousness) and the Fear of COVID-19 Scale. Adherence to COVID-19 precautions (ACP) was self-reported and scored as the number of preventive measures adopted (0–11).

Results: Of 4,477 responses, 4,011 participants were included after removing duplicates and incomplete entries (56.4% female; n=2,261). Mean (SD) ACP score was 5.99 (2.25) (median 6.0). Adherence was higher among females; those with a university degree; married participants; those not living in a separated/divorced family structure; those reporting good income; participants with chronic disease; non-smokers and non-drinkers; and those reporting a COVID-19 related death in their family or close social circle. Higher perceived contagiousness was associated with greater adoption of preventive measures, with perceived dangerousness and fear mediating this relationship.

Conclusion: Public health efforts that strengthen accurate perceptions of infectious disease dangerousness and contagiousness, and address related fear, may increase use of protective measures and help reduce transmission in future pandemics.

Keywords: COVID-19, Risk Perception, Fear, Adults, Türkiye

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INTRODUCTION

Since its emergence in late 2019, the COVID-19 pandemic has profoundly impacted global public health, resulting in over 7 million deaths worldwide (1). In the absence of widespread vaccination during the earlier phases of the crisis, non-pharmaceutical interventions and public health measures served as the primary strategies to mitigate viral transmission (2). However, the efficacy of these public health initiatives relies heavily on public compliance. Prior literature indicates that adherence to preventive behaviors is influenced by socio-demographic characteristics such as sex, education level, and employment status as well as individual cognitive appraisals, most notably the perception of the disease itself (3,4).

Disease perception is closely linked to epidemiological severity indicators, including transmission rates and lethality. During the specific pandemic phase of this study in early 2021, Türkiye had recorded substantial disease metrics, contributing to a global landscape where case fatality rates fluctuated widely between 0.95% and 14.10% depending on variant dynamics and localized healthcare capacities (5). While the objective threat of COVID-19 was severe, individual subjective interpretations of the virus varied markedly. Extant research demonstrates that individuals who appraise a disease as highly contagious and severe are significantly more likely to adhere to health recommendations (6,7).

In addition to cognitive risk appraisals, emotional responses, particularly health-related fear, represent a critical determinant of behavioral compliance (8). Driven by continuous media exposure, economic instability, and the localized impact of mortality within communities, public anxiety and fear regarding viral transmission escalated rapidly during the initial waves of the pandemic (9,10). While standard preventative indices often focus exclusively on clinical behaviors (such as masking and hand hygiene), public health compliance during prolonged crises frequently encompasses a broader spectrum of health-protective adjustments, including lifestyle modifications like regular sleep and physical exercise to preserve immune health. To date, several investigations have explored individual compliance with pandemic regulations (11,12). However, the specific pathways linking cognitive disease appraisals, emotional fear responses, and holistic protective behaviors during critical phases of the pandemic require further clarification. Crucially, given the cross-sectional nature of current behavioral data, these relationships are best understood as complex statistical associations rather than strict causal chains.

With this in mind, this study examined the statistical indirect associations among disease perception, fear, and behavioral adherence. We hypothesized that higher perceived contagiousness would be positively associated with an index of precaution adherence, and that this relationship would be sequentially mediated by perceived dangerousness and fear of the virus. Consequently, the objective of this study was to evaluate the socio-demographic and perceptual factors associated with compliance

with preventive measures within a sample of adults in Türkiye.

METHOD

This cross-sectional study was conducted in Türkiye between March 1 and April 1, 2021. Ethical approval was obtained from the Non-Interventional Clinical Research Ethics Committee of Eskişehir Osmangazi University University (Approval Number: 25403353; Date: 09.02.2021).

Data collection was executed using an online questionnaire hosted on Google Forms. Due to pandemic-related restrictions during this specific phase, participants were recruited via non-probability convenience and snowball sampling methods through digital platforms. Consequently, the sample is not fully representative of the general Turkish population and primarily reflects an online-accessible demographic. A total of 4477 responses were received. After excluding 466 duplicate or incomplete submissions, the final sample consisted of 4011 adults (aged 18 years and over) residing across 78 of the 81 provinces in Türkiye.

A structured questionnaire was compiled based on existing literature (13,14), encompassing socio-demographic characteristics, cognitive disease perceptions, emotional fear responses, and preventive behaviors.

COVID-19 Disease Perception Scale, developed by Genis et al. (15), is a 5-point Likert-type scale that measures two distinct sub-dimensions: Dangerousness (3 items; evaluating personal risk perception) and Contagiousness (4 items; evaluating transmission risk). Sub-dimension scores are calculated by averaging item responses, yielding scores from 1 to 5. Higher scores indicate heightened risk perceptions.

COVID-19 Fear Scale was developed by Ahorsu et al. (16) and adapted into Turkish by Satici et al. (17) in 2020. This 7-item, 5-point Likert-type scale measures the fear of COVID-19. Items are summated to create a total score ranging from 7 to 35, where higher values reflect greater fear.

To evaluate behavioral compliance, an 11-item Adherence to COVID-19 Precautions (ACP) Index was compiled from recommendations issued by the Turkish Ministry of Health and available literature (18,19). Cultivating a holistic perspective on pandemic mitigation, the index sums public clinical safety measures (such as hand hygiene, mask use, and physical distancing) alongside health-protective lifestyle modifications (such as sanitizing packages, maintaining regular sleep, exercise, and balanced nutrition). Affirmative behaviors were scored as 1 and non-adoption as 0, yielding a bounded count score from 0 to 11. Combining these heterogeneous items into a singular index provides a comprehensive indicator of overall health-protective compliance during prolonged crisis contexts. In this sample, the 11-item index demonstrated acceptable internal consistency, with a Cronbach alpha coefficient of .77.

Family income status was subjectively classified by participants as either good or bad. Smoking status was defined as smoking at least one cigarette per day, and alcohol consumption was defined as drinking at least once per week. Participants

raised by a single parent due to parental divorce, separation, or death were categorized under a separated/divorced family structure.

Statistical Analysis

Data were exported from Google Forms and analyzed using IBM SPSS statistical package program. For univariate analyses, independent-samples t-tests and one-way Analysis of Variance (ANOVA) with Tukey HSD post-hoc tests were used to examine differences in raw ACP scores across groups. Because the ACP Index is a bounded count outcome exhibiting significant positive skewness, standard linear regression assumptions were initially violated. To address this distribution constraint and satisfy parametric prerequisites, the ACP Index scores were transformed using a base-10 logarithm. A multiple linear regression analysis via the Enter method was then executed to identify independent predictors of the log-transformed ACP Index, controlling for essential socio-demographic confounders (age, sex, education, income, family structure, chronic disease history, smoking, and alcohol use).

To examine the underlying mechanisms without implying longitudinal causality, a cross-sectional serial mediation analysis was performed using Hayes PROCESS macro Model 6 (20). This model evaluated the statistical indirect associations of Contagiousness (X) on Adherence (Y) sequentially through Dangerousness (M1) and Fear (M2). Standardized coefficients, standard errors, and total, direct, and indirect pathways were computed. Significance was evaluated using 5000 bootstrap resamples to construct 95 percent percentile bootstrap confidence intervals (CI), where an interval excluding zero denoted statistical significance. The alpha level for all tests was established at p less than or equal to .05. In accordance with standard reporting guidelines, exact p-values are reported, with values recorded by SPSS as .000 corrected to p less than .001.

RESULTS

Among the final analyzed sample (N = 4011), 56.4 percent (n = 2261) were female and 43.6 percent (n = 1750) were male. Participant ages spanned from 18 to 85 years, with a young sample bias reflected in a mean age of 26.22 years (SD = 10.59). Consistent with the online convenience sampling method utilized, the sample was also predominantly composed of highly educated individuals and those reporting good subjective family income.

The raw ACP Index scores ranged from 0 to 11, with a mean score of 5.99 (SD = 2.25) and a median score of 6.0. **Table 1** presents the full distribution of the socio-demographic characteristics and their univariate associations with the ACP Index.

Overall, 99.2 percent of the participants reported practicing at least one protective behavior against COVID-19. The most prevalent precautions adopted were mask usage (96.1 %), hand hygiene (93.9 %), and physical distancing (89.0 %). **Table 2** displays the distribution of these health-protective behaviors alongside corresponding scores for disease perception and fear.

A small subset of the sample (n = 39) reported receiving no information regarding COVID-19. Among those who did, the primary sources of

Table 1. The distribution of the ACP index scores according to sociodemographic characteristics and related variables

Sociodemographic Characteristics and Related Variables	n	%	Mean scores from the ACP Index ± SD	Test statistic (t/F)	p-Value
Sex					
Female	2261	56.4	6.25 ± 2.09	**8.068**	**<0.001**
Male	1750	43.6	5.66 ± 2.41		
Age Groups (years)					
25 and below	2738	68.3	6.02± 2.25	0.685	0.504
26-35	577	14.4	5.90± 2.17		
36 and above	696	17.4	5.97 ± 2.32		
Education Status					
High School and Below	1348	33.6	5.87 ± 2.31	**2.475**	**0.013**
University and Above	2663	66.4	6.06 ± 2.22		
Working Status					
Working	1309	32.6	6.07 ± 2.38	1.410	0.159
Not Working	2702	67.4	5.96 ± 2.18		
Marital Status					
Married	1006	25.1	6.26 ± 2.13	**4.380**	**<0.001**
Not Married	3005	74.9	5.90 ± 2.28		
Family Type					
Nuclear Family [a]	3387	84.4	6.05 ± 2.24	**7.627**	**<0.001**
Extended Family [b]	416	10.4	5.70 ± 2.27		
Separated/divorced family structure[b]	208	5.2	5.62 ± 2.30		
Family Income Status					
Bad	215	5.4	5.52 ± 2.37	**3.163**	**0.002**
Good	3796	94.6	6.02 ± 2.24		
Presence of a Healthcare Worker in the Family					
Not Present	3141	78.3	5.94 ± 2.24	**3.031**	**0.003**
Present	870	21.7	6.20 ± 2.26		
The Place of Residence					
City Center	2064	51.5	6.01 ± 2.20	1.742	0.175
County	1603	40.0	6.02 ± 2.27		
Village	344	8.5	5.78 ± 2.42		
Chronic Disease History Requiring Continuous Medication					
Not Present	3606	89.9	5.95 ± 2.27	**3.233**	**0.001**
Present	405	10.1	6.34 ± 1.99		
Smoking Status					
Non-smoker	2815	70.2	6.11 ± 2.21	**5.155**	**<0.001**
Smoker	1196	29.8	5.71 ± 2.31		
Alcohol Consumption Status					
Non-consumer	3658	91.2	6.05 ± 2.21	**5.066**	**<0.001**
Consumer	353	8.8	5.35 ± 2.50		
History of COVID-19					
Not Present	3397	84.7	5.99 ± 2.26	0.249	0.804
Present	614	15.3	6.01 ± 2.21		
History of COVID-19 in Family Members					
Not Present	2827	70.5	5.98 ± 2.29	0.495	0.621
Present	1184	29.5	6.02 ± 2.16		
History of Death Due to COVID-19 in Family and Close Circle					
Not Present	2795	69.7	5.95 ± 2.32	**2.038**	**0.042**
Present	1216	30.3	6.10 ± 2.07		
Total	4011	100.0	5.99 ± 2.25		

Table 2. The Distribution of Precautions Taken Against COVID-19 In The Study Group

Protective Measures	n	%
Hand hygiene	3768	93.9
Cleaning house	2561	63.8
Ventilating the living space frequently	3077	76.7
Mask use	3854	96.1
Physical distancing	3570	89.0
Wearing gloves	1128	28.1
Healthy eating	2030	50.6
Regularly sleeping	1288	32.1
Doing exercises	1019	25.4
Keeping packages outside the home for a while	1721	42.9
Other	21	0.5
None	33	0.8
Total	4011	100.0

Table 3. The Distribution of Information Sources Regarding COVID-19 In The Study Group

Information Sources	n	%
Television	3391	84.5
Book/Newspaper/Magazine/Brochure	1337	33.3
Social Media	3390	84.5
Healthcare Workers	2097	52.3
Scientific Publications	1510	37.7
Training/Education	951	23.7
Close circle/Friends/Relatives	2239	55.8
None	39	1.0
Total	4011	100.0

information were television, social media, and immediate social circles (friends, relatives), respectively. The complete breakdown of pandemic information sources is presented in **Table 3**.

Total scores on the COVID-19 Fear Scale ranged from 7 to 35, with a mean score of 17.57 (SD = 6.21, median = 17). For the COVID-19 Disease Perception Scale, the mean score for the dangerousness sub-dimension was 3.91 (SD = 0.01, median = 4.0), and the mean score for the contagiousness sub-dimension was 3.78 (SD = 0.01, median = 4.0). The statistical relationships among cognitive disease perceptions, emotional fear, and the raw ACP Index are shown in (**Table 4)**. Although the correlations between these perception variables and the ACP Index reached statistical significance due to the high statistical power afforded by the large sample size, the absolute correlation coefficients were weak.

To identify the independent socio-demographic and health factors predicting the log-transformed ACP Index, a multiple linear regression analysis was conducted. The multivariable model significantly predicted the outcome, with an F-value of 13.42, a p-value less than .001, and an R-squared value of .036. The individual coefficients, standard errors, and confidence intervals for each predictor are detailed in (**Table 5)**. According to the model, sex, education level, marital status, extended family type, chronic disease history, and alcohol consumption were significant independent predictors of the ACP Index, with p-values less than .05 for each.

The cross-sectional serial mediation analysis (Hayes PROCESS Model 6) evaluated the indirect pathways linking contagiousness perception (X) and adherence (Y) through dangerousness perception (M1) and fear (M2). As presented in (**Table 6)**, all direct pathways within the path model were statistically significant (p less

Table 4. The relationship between scores obtained from COVID-19 Disease Perception Scale, COVID-19 Fear Scale and Adherence to COVID-19 precautions index

	COVID-19 Contagiousness Perception	COVID-19 Dangerousness Perception	Fear of COVID-19	Adherence to COVID-19 Precautions
COVID-19 Contagiousness Perception	1	0.438	0.319	0.155
COVID-19 Dangerousness Perception	0.438	1	0.312	0.155
Fear of COVID-19	0.319	0.312	1	0.172
Adherence to COVID-19 Precautions	0.155	0.180	0.172	1
p values are less than 0.001 for each.				

Table 5. Multiple Linear Regression Analysis Predicting ACP Index

Predictor	B	SE	β	t	p	95% CI
(Constant)	0.815	0.041		19.995	< 0.001	[0.735, 0.895]
Sex (Reference: Male)	-0.043	0.007	-0.103	-6.280	< 0.001	[-0.057, -0.030]
Age	0.000	0.000	-0.011	-0.691	0.489	[-0.001, 0.000]
Education Level (Reference: High School and Below)	0.025	0.007	0.057	3.465	0.001	[0.011, 0.039]
Marital Status (Reference: Married)	-0.036	0.008	-0.075	-4.516	< 0.001	[-0.051, -0.020]
Extended Family Type (Reference: Nuclear Family)	-0.031	0.011	-0.046	-2.904	0.004	[-0.052, -0.010]
Separated/divorced family structure (Reference: Nuclear Family)	-0.027	0.015	-0.029	-1.835	0.067	[-0.057, 0.002]
Income Status (Reference: Low Income)	0.028	0.015	0.030	1.889	0.059	[-0.001, 0.056]
Healthcare Worker in Family (Reference: Present)	< 0.001	0.000	0.019	1.225	0.221	[0.000, 0.000]
Chronic Disease History (Reference: Not Present)	0.027	0.011	0.039	2.425	0.015	[0.005, 0.048]
Smoking (Reference: Smoker)	-0.008	0.008	-0.019	-1.107	0.268	[-0.023, 0.007]
Alcohol (Reference: Drinker)	-0.048	0.012	-0.065	-3.928	<0.001	[-0.072, -0.024]
Model fit statistics: R = .189, R Square = .036, Adjusted R Square = .033, F(11, 3966) = 13.42, p < .001, Durbin-Watson = 0.98.						

Table 6. Model Pathways, Direct, and Indirect Effects for the Serial Mediation Mode

Model Pathways & Effects	Unstandardized Coefficient (B)	Standard Error (SE)	t / Z	p-value	95% CI	Standardized Coefficient (β)
Direct Pathways						
Contagiousness (X) → Dangerousness (M1)	.328	.011	30.821	< .001	[.307, .349]	.438
Contagiousness (X) → Fear (M2)	1.296	.094	13.836	< .001	[1.112, 1.479]	.226
Dangerousness (M1) → Fear (M2)	1.637	.125	13.109	< .001	[1.392, 1.882]	.214
Contagiousness (X) → Adaptation (Y) (Direct Effect)	.143	.036	3.928	< .001	[.072, .215]	.069
Danger (M1) → Adaptation (Y)	.318	.049	6.548	< .001	[.222, .412]	.115
Fear (M2) → Adaptation (Y)	.041	.006	6.867	< .001	[.029, .053]	.114
Total & Indirect System Effects						
Total Effect (X→Y)	.323	.032	9.952	< .001	[.259, .387]	.155
Total Indirect Effect	.180	.019	—	—	[.143, .218]	.086
*** Indirect Path 1: X→M1→Y**	.104	.017	—	—	[.071, .138]	.050
*** Indirect Path 2: X→M2→Y**	.053	.009	—	—	[.036, .072]	.026
*** Indirect Path 3 (Serial): X→M1→M2→Y**	.022	.004	—	—	[.015, .030]	.011

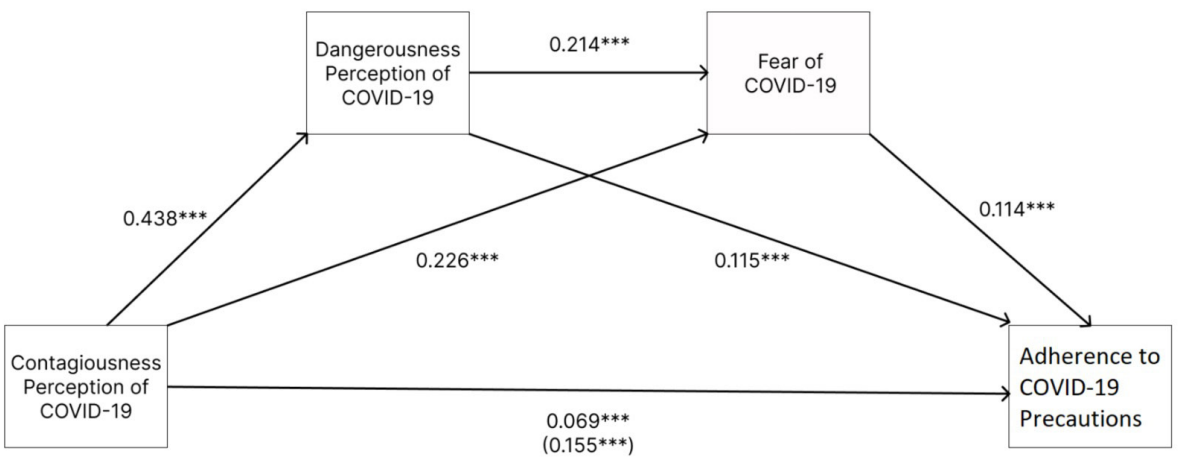

Figure 1. The serial mediation model of Contagiousness perception of COVID-19 through the dangerousness perception of COVID-19 and fear of COVID-19 on adherence to COVID-19 precautions with standardized regression coefficients (p<0.001 for each path). Total effect of contagiousness perception on adherence to precautions were given in parenthesis

than .001). The total effect of contagiousness perception on precaution adherence was statistically significant (B = .323, SE = .032, p less than .001). When controlling for both mediators, the direct effect of contagiousness perception on adherence remained significant (B = .143, SE = .036, p less than .001), indicating a pattern of partial mediation.

Crucially, the total indirect effect was significant (B = .180, BootSE = .019, 95 percent bootstrap CI [.143, .218]). The hypothesized serial mediation chain (X to M1 to M2 to Y) was fully supported, showing a significant indirect association (B = .022, BootSE = .004, 95 percent bootstrap CI [.015, .030]). This confirms that higher perceived contagiousness is associated with an elevated perception of dangerousness, which sequentially relates to heightened fear and, ultimately, greater precaution adherence. The complete model with standardized regression coefficients is visually diagrammed in (**Figure 1)**.

DISCUSSION

The COVID-19 pandemic caused profound global disruptions, severely impacting populations through high morbidity, mortality, strict quarantine protocols, and sudden socio-economic adjustments. During prolonged public health crises, widespread compliance with non-pharmaceutical interventions such as hand hygiene, facial masks, and physical distancing serves as the primary line of defense against community transmission. However, individual adherence to these guidelines is heavily dictated by cognitive disease perceptions and emotional risk responses. Understanding these underlying behavioral mechanisms provides public health professionals with crucial data to design effective intervention strategies for future respiratory pandemics (6).

In the present study, the most frequently adopted preventive behaviors were mask usage, hand hygiene, and physical distancing, respectively. This widespread adoption reflects the robust visibility of public health campaigns initiated by the Turkish Ministry of Health (18). In comparison, international literature demonstrates variations in specific behavioral priorities. For instance, Narayana et al. identified hand hygiene, respiratory etiquette (sneezing into the elbow), and mask compliance as the primary actions in their sample, while Sulistyawati et al. reported high rates of respiratory etiquette, private vehicle usage, and mask wearing (21,22). These cross-cultural variations highlight how differing national information channels, governmental mandates, and socio-cultural contexts shape public compliance patterns.

Socio-demographic factors also emerged as important independent predictors of adherence. In this sample, females exhibited significantly higher compliance with precautions than males, which aligns with international patterns reported by Clark et al. and Recio-Vivas et al. (23,24) While some researchers, such as Yan et al., observed no distinct gender differences in adherence, a broad consensus suggests that women generally display higher risk-aversion and greater compliance with health guidelines (25). Interestingly, univariate analysis revealed no significant variations across age groups, contrasting with evidence from Recio-Vivas et al. indicating enhanced compliance among older adults (24). Given that males and older populations face a heightened clinical risk for severe COVID-19 pathology, their lower or

static adherence rates emphasize the need to target these demographics with tailored health communications.

Educational attainment and socio-economic positioning further influenced compliance. Higher education levels significantly predicted increased adherence to precautions, a finding echoed in prior studies(27,28). Higher education is often tied to enhanced health literacy and critical thinking skills, enabling individuals to process complex epidemiological data and comprehend the long-term utility of preventive measures. Similarly, participants who evaluated their family income status as good demonstrated superior adherence compared to those reporting poor financial status. This reinforces evidence from Zaildo et al. and Lee et al., who highlighted that financial insecurity acts as a structural barrier to compliance(28, 29). Individuals from lower-income backgrounds often lack the financial flexibility to purchase personal protective equipment or alter their daily routines, forcing them to prioritize immediate economic survival over health-protective adherence.

Furthermore, household and lifestyle factors played a distinct role in behavioral compliance. Participants living within nuclear or extended family structures reported higher adherence than those from separated or divorced family structures. Co-residence with family members likely fosters a sense of collective responsibility, where individuals adhere to safety protocols to shield vulnerable relatives from infection, a dynamic supported by Li and Xu (30). Conversely, health-compromising behaviors like smoking and alcohol consumption were associated with reduced adherence to precautions. Substance use often co-occurs with elevated impulsivity and a generalized tolerance for behavioral risk(31). Our findings mirror those of Monnig et al., who identified lower compliance among regular alcohol consumers, and Mendoza-Jimenez et al., who noted that lifestyle risk factors correlate with poor adherence to basic hygienic measures(32,33).

Beyond descriptive demographics, this study illuminated the psychological pathways that drive protective behaviors. Prior research in diverse cultural settings has consistently linked risk perceptions to compliance. For example, Yan et al. (25,34)v demonstrated that high compliance rates in Hong Kong were driven by perceived benefits and self-efficacy, while Roberts and David found that fear of the virus significantly prompted health-seeking behaviors and precaution adoption among American college students. Additionally, Recio-Vivas et al. (24) vestablished that elevated infection risk perception directly catalyzed preventive action in Spain.

The results of our cross-sectional serial mediation analysis expand on these findings by mapping the statistical indirect pathways among these cognitive and emotional variables. In our model, higher contagiousness perception was associated with an increased perception of disease dangerousness, which sequentially related to heightened fear, ultimately predicting greater adherence to precautions. It is critical to note that due to the very large sample size of this study, the bivariate correlations between these psychometric scores and the final adherence index were weak in absolute magnitude. Nevertheless, the multivariable and mediation models show that cognitive appraisal of transmission risk (contagiousness) acts as an initial trigger that amplifies personal vulnerability assessments (dangerousness). This cognitive evaluation feeds

into an emotional response (fear), which serves as a proximal motivator for health-protective compliance. This underscores the psychological reality that facts alone (contagiousness) are often filtered through subjective risk and emotional salience before translating into protective behavioral actions.

Limitations of the Study

Several limitations must be acknowledged when interpreting these findings. First, due to the strict quarantine and mobility restrictions enforced during the pandemic, data collection relied entirely on an online questionnaire distributed via convenience and snowball sampling. Because the data were collected during a brief period between March and April 2021, the results are only reflective of that specific timeframe. Consequently, the sample is heavily skewed toward younger, highly educated, and internet-accessible demographics, meaning these findings cannot be generalized to the broader, non-digital population of Türkiye. Second, because this study utilized a cross-sectional design, all measures were collected simultaneously. Therefore, the paths identified in the serial mediation model represent statistical associations and indirect patterns within a single timepoint; they cannot be used to infer true longitudinal causality or temporal precedence. Third, all behavioral data were collected via self-report measures, which are susceptible to social desirability bias and memory recall errors, potentially leading to an overestimation of compliance rates. Finally, while the 11-item Adherence to COVID-19 Precautions Index demonstrated acceptable internal consistency in this sample, it grouped clinical prevention items alongside general healthy lifestyle habits, which may capture broad self-care tendencies rather than pandemic-specific compliance.

CONCLUSION

In conclusion, this study demonstrates that adherence to COVID-19 precautions was moderate to high, driven by elevated perceptions of disease dangerousness and contagiousness, alongside moderate levels of fear. Increased compliance was independently predicted by female sex, higher educational attainment, stable family structures, higher subjective income, and a history of chronic disease, whereas smoking and alcohol consumption predicted lower compliance. Crucially, the cross-sectional mediation analysis supported the hypothesis that the association between transmission risk perception and behavioral compliance is partially mediated through dangerousness perception and emotional fear.

These findings offer practical insights for public health governance. To optimize compliance during future infectious disease outbreaks, public health campaigns should move beyond merely broadcasting transmission rates. Instead, interventions should focus on clearly communicating the clinical dangerousness of the pathogen while providing transparent, actionable guidelines to build public self-efficacy. Because psychological risk pathways vary across demographics, future communication frameworks must prioritize vulnerable, low-adherence sub-groups—specifically males, lower-income populations, and individuals exhibiting generalized risk-taking behaviors—to ensure equitable protection across society. Finally, future research should utilize longitudinal designs and representative, probability-based sampling methods to track how these cognitive-emotional pathways evolve over the course of an extended public health crisis.

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

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Ethical permission was obtained from the Eskişehir Osmangazi University, Medical Faculty Clinical / Human Research Ethics Committee for this study with date 09.02.2021 and number 25403353,v and Helsinki Declaration rules were followed to conduct this study.

Previous Presentation

Some part of this study was presented as oral presentation at "Union of Thrace Universities IV. International Health Sciences Congress" held in Kırklareli city, entitled as "Assessment of COVID-19 Perception and Fear in Adults".

Author Contributions

Concept: AK, AÜ, DA, Design: AK, AÜ, DA, Supervising: AK, AÜ, DA, Financing and equipment: AK, AÜ, DA, Data collection and entry: AK, AÜ, DA, Analysis and interpretation: AK, AÜ, DA, Literature search: AK, AÜ, DA, Writing: AK, AÜ, DA, Critical review: AK, AÜ, DA

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Research Article

Co-Mutation Landscape of PIK3CA Across Multiple Adenocarcinomas: Insights from TCGA Data

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Abstract

Objective: PIK3CA is one of the most frequently mutated oncogenes across multiple cancer types, playing a crucial role in tumorigenesis via the PI3K/AKT/mTOR signaling pathway. Understanding its genuine co-mutation landscape is essential for identifying oncogenic interactions and refining targeted therapeutic strategies. In this study, we analyzed the true functional co-mutation patterns of PIK3CA in colorectal adenocarcinoma (COAD), cervical squamous cell carcinoma and endocervical adenocarcinoma (CESC), stomach adenocarcinoma (STAD), and lung adenocarcinoma (LUAD).

Method: Somatic mutation data were obtained from The Cancer Genome Atlas (TCGA). Co-mutation and mutual exclusivity analyses were performed using R (maftools). To rigorously distinguish genuine biological cooperativity from confounding background mutation rates, multivariate logistic regression models were implemented, incorporating tumor mutational burden (TMB) as a continuous covariate.

Results: TMB-adjusted analyses revealed distinct, robust co-occurrence and mutual exclusivity relationships across cancer types, filtering out passenger mutations. In COAD, PIK3CA mutations significantly co-occur with KRAS, suggesting a cooperative role in tumorigenesis, while maintaining strict mutual exclusivity with TP53. In STAD, PIK3CA exhibits a strong, true functional co-occurrence with the chromatin remodeling gene ARID1A, while maintaining mutual exclusivity with TP53 and CSMD3. Interestingly, in both LUAD and CESC, PIK3CA demonstrates a highly significant mutual exclusivity with the mucin gene MUC17, pointing to context-specific evolutionary trajectories.

Conclusion: These findings highlight the complex, TMB-independent molecular landscape of PIK3CA-driven tumors, emphasizing the necessity of cancer-type-specific therapeutic approaches. By utilizing robust TMB-adjusted models, this study successfully isolates true genetic interactions, providing valuable insights into potential drug resistance mechanisms and novel combination therapy strategies for PIK3CA-mutant cancers.

Keywords: PIK3CA, Co-Mutation Analysis, TCGA, Cancer Genomics, Precision Onv vcology

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INTRODUCTION

Cancer is a multifactorial disease triggered by genetic and epigenetic alterations, which disrupt fundamental cellular pathways. PIK3CA is one of the most frequently mutated genes across multiple cancer types(1). This gene encodes the catalytic subunit of the enzyme phosphatidylinositol 3-kinase (PI3K). PI3K is a crucial component of the PI3K/AKT/mTOR signaling pathway, which regulates critical processes such as cellular proliferation, survival, and metabolism(2). Alterations in this pathway lead to an uncontrolled increase in cellular growth and the development of resistance to apoptosis, thereby causing tumor development(3). Therefore, PIK3CA mutations are of great importance in cancer research and have yielded significant implications for personalized cancer therapy.

PIK3CA mutations have been detected in various human cancers, such as colorectal adenocarcinoma (COAD), cervical squamous cell carcinoma and endocervical adenocarcinoma (CESC), stomach adenocarcinoma (STAD), and lung adenocarcinoma (LUAD)(3). These mutations typically occur in hotspot regions such as E542K, E545K, and H1047R, leading to the constitutive activation of the PI3K pathway(4). Although PIK3CA alterations are sometimes sufficient on their own to trigger oncogenesis, their effects are generally modulated by concurrent mutations in other oncogenes and tumor suppressor genes(5). Despite an increasing understanding of PIK3CA-driven oncogenesis, challenges remain in effectively targeting this pathway, such as complex regulatory mechanisms that limit the efficacy of single-agent therapies. Furthermore, concurrent mutations in genes such as TP53, PTEN, and KRAS affect tumor behavior and treatment responses, emphasizing the importance of comprehensive molecular profiling in the field of individualized therapy(6). Therefore, understanding the co-mutation relationships of PIK3CA is crucial for elucidating its role in different cancer types and identifying potential treatment strategies.

Co-mutation analysis is a powerful approach to uncover functional interactions among oncogenic factors. The presence of concurrent mutations indicates cooperative oncogenic mechanisms, whereas mutually exclusive mutations may point to alternative tumorigenic pathways. For instance, PIK3CA mutations frequently co-occur with KRAS in colorectal cancer, suggesting a potential crosstalk between the PI3K and MAPK signaling pathways(7). In some cancers, however, the mutual exclusivity between PIK3CA and TP53 mutations may indicate that tumors rely on distinct oncogenesis mechanisms(8,9). Such information is critical in the development of targeted therapies, as it enables the prediction of drug sensitivity or resistance based on mutational profiles.

Large-scale cancer genome studies, and particularly initiatives like The Cancer Genome Atlas (TCGA), have provided unique opportunities to systematically investigate co-mutation patterns. By utilizing TCGA data, researchers can identify statistically significant concurrent and mutually exclusive mutations across various cancer types. These analyses can help define molecular subtypes of cancer, improve patient stratification for targeted therapies, and uncover therapeutic vulnerabilities.

Given the clinical significance of PIK3CA mutations and their potential interactions with other oncogenic alterations, this study aims to comprehensively investigate the co-mutation interactions of PIK3CA across four different

cancer types. Using TCGA data, we aim to identify significant concurrent and mutually exclusive mutations, evaluate their potential functional impacts, and elucidate their relationship with current treatment strategies. Understanding these co-mutation patterns will contribute to refining precision medicine approaches, guiding the development of combination therapies, and ultimately improving clinical outcomes for patients harboring PIK3CA mutations.

METHOD

To analyze the co-mutations of PIK3CA across four different cancer types (COAD, CESC, STAD, and LUAD), we utilized the TCGA database. Mutation data were retrieved from TCGA and processed using R (v4.4.3) to obtain accurate and reproducible results.

Data Collection and Preprocessing

Mutation data (Simple Nucleotide Variation, Masked Somatic Mutation) for the selected cancer types were obtained from TCGA using the TCGAbiolinks R package(10). Specifically, the "Aliquot Ensemble Somatic Variant Merging and Masking" workflow was utilized to download the data (accessed in July 2026). This package allows for the efficient querying, downloading, and preprocessing of TCGA data. To ensure consistency, only samples containing available PIK3CA mutation information were included in the study.

Mutation Analysis and Annotation

The downloaded mutation data were processed using R (v4.4.3) and annotated using the maftools R package(11). Consistent with standard maftools processing parameters, silent mutations were automatically filtered out; therefore, only non-silent variants (e.g., missense, nonsense, frame-shifts, and splice-site mutations) were retained for downstream analyses. No additional custom variant allele frequency (VAF) thresholds were applied. This package facilitates comprehensive mutation annotation, allowing for the identification of frequently mutated genes and their corresponding mutation types. To facilitate comparative analyses, PIK3CA mutant and wild-type groups were defined.

Co-Mutation and Confounding Analysis

For each cancer type, the top 20 most frequently mutated genes were determined using maftools. Initial co-occurrence and mutual exclusivity patterns were evaluated and visualized using the "somaticInteractions" function from the maftools package, which employs Fisher's exact test. To rigorously account for confounding effects driven by high background mutation rates, such as tumor mutational burden (TMB) and microsatellite instability (MSI) phenotypes, a multivariate logistic regression model was implemented using the base R "glm" function. In these models, the mutational status of PIK3CA was evaluated as the dependent variable, with the mutational status of each candidate gene serving as the independent variable. The total TMB (calculated as total mutations per sample, log10-transformed) was incorporated into the models as a continuous covariate. This approach allowed us to successfully distinguish genuine functional cooperativity from a shared dependence on global mutation burden. A significance threshold of $p < 0.05$ was established for the TMB-adjusted associations.

Visualization and Statistical Validation

Co-occurrence and mutual exclusivity relationships were visualized using heatmaps generated by the "somaticInteractions" function. To clearly represent the mutation patterns, oncoprint plots were generated using the ComplexHeatmap package(12). These plots

illustrate the distribution of PIK3CA mutations alongside the top 20 most frequently mutated genes across the samples, providing insights into potential interactions.

RESULTS

In COAD, after adjusting for tumor mutational burden (TMB), PIK3CA (30% prevalence) mutations demonstrated a robust and statistically significant co-occurrence with KRAS ($p < 0.001$, OR = 2.46). Furthermore, a strong mutual exclusivity between PIK3CA and TP53 was observed ($p = 0.006$, OR = 0.56) independent of mutational background **(Figure 1A)**. Oncoprint analysis revealed that PIK3CA mutations were predominantly missense mutations, with rare overlapping mutational events with TP53 **(Figure 1B)**.

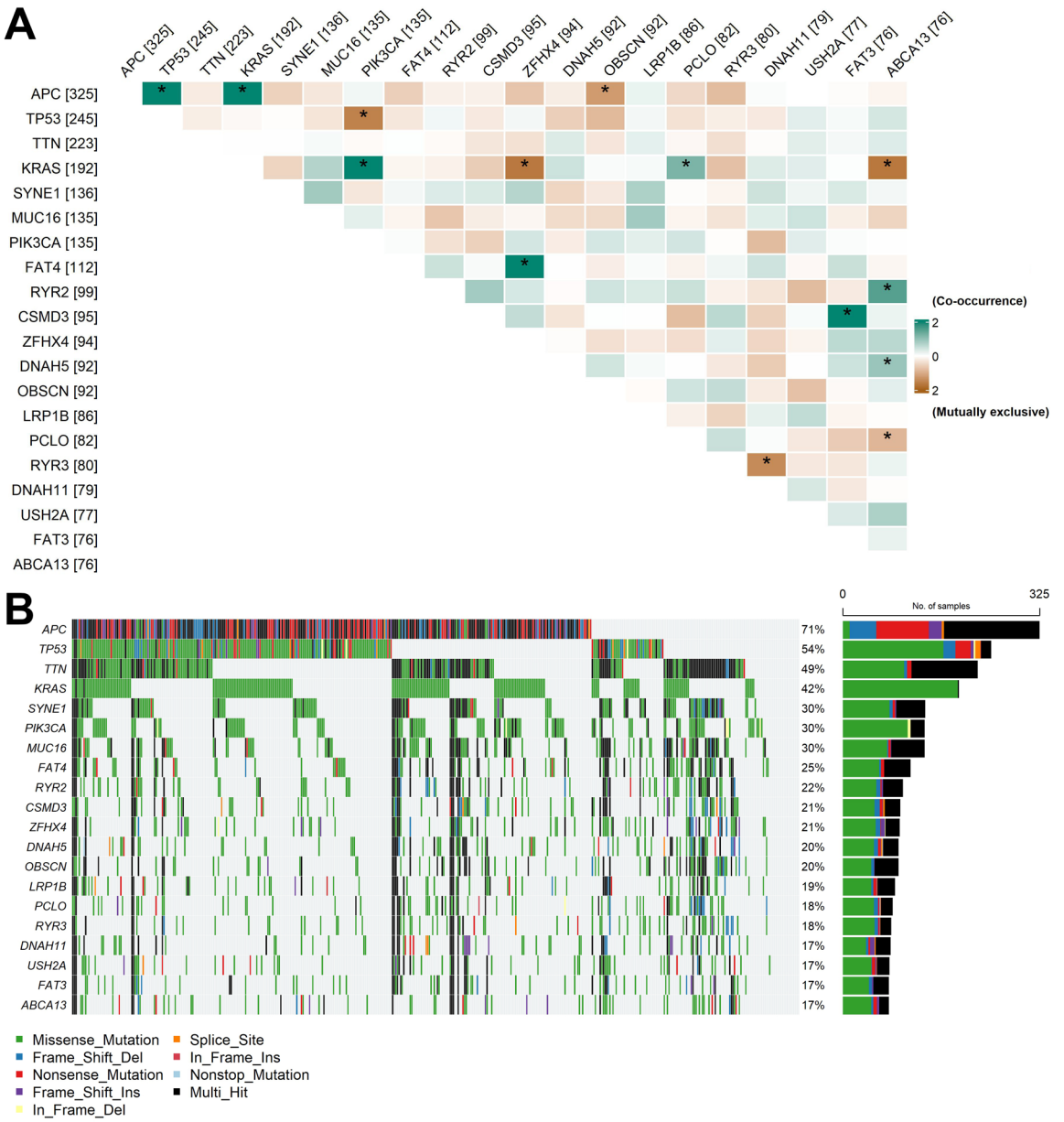

Figure 1. (A) Co-Mutation and Mutual Exclusivity Patterns of PIK3CA in COAD (green: co-occurrence; brown: mutual exclusivity) **(B)** Mutational Landscape of COAD.

In CESC, following TMB adjustment, PIK3CA (28% prevalence) mutations exhibited a highly significant mutual exclusivity with the mucin gene MUC17 (p = 0.009, OR = 0.21) and the calcium channel gene RYR2 (p = 0.048, OR = 0.35) **(Figure 2A)**. Oncoprint analysis revealed that PIK3CA mutations were distributed across the cohort without forming distinct clusters with classical structural driver mutations **(Figure 2B)**.

In STAD, TMB-adjusted logistic regression highlighted a distinct mutational landscape for PIK3CA (16% prevalence). The chromatin remodeling gene ARID1A showed a highly significant, functional co-occurrence with PIK3CA (p = 0.0004, OR = 3.30). Additionally, PIK3CA mutations exhibited strict mutual

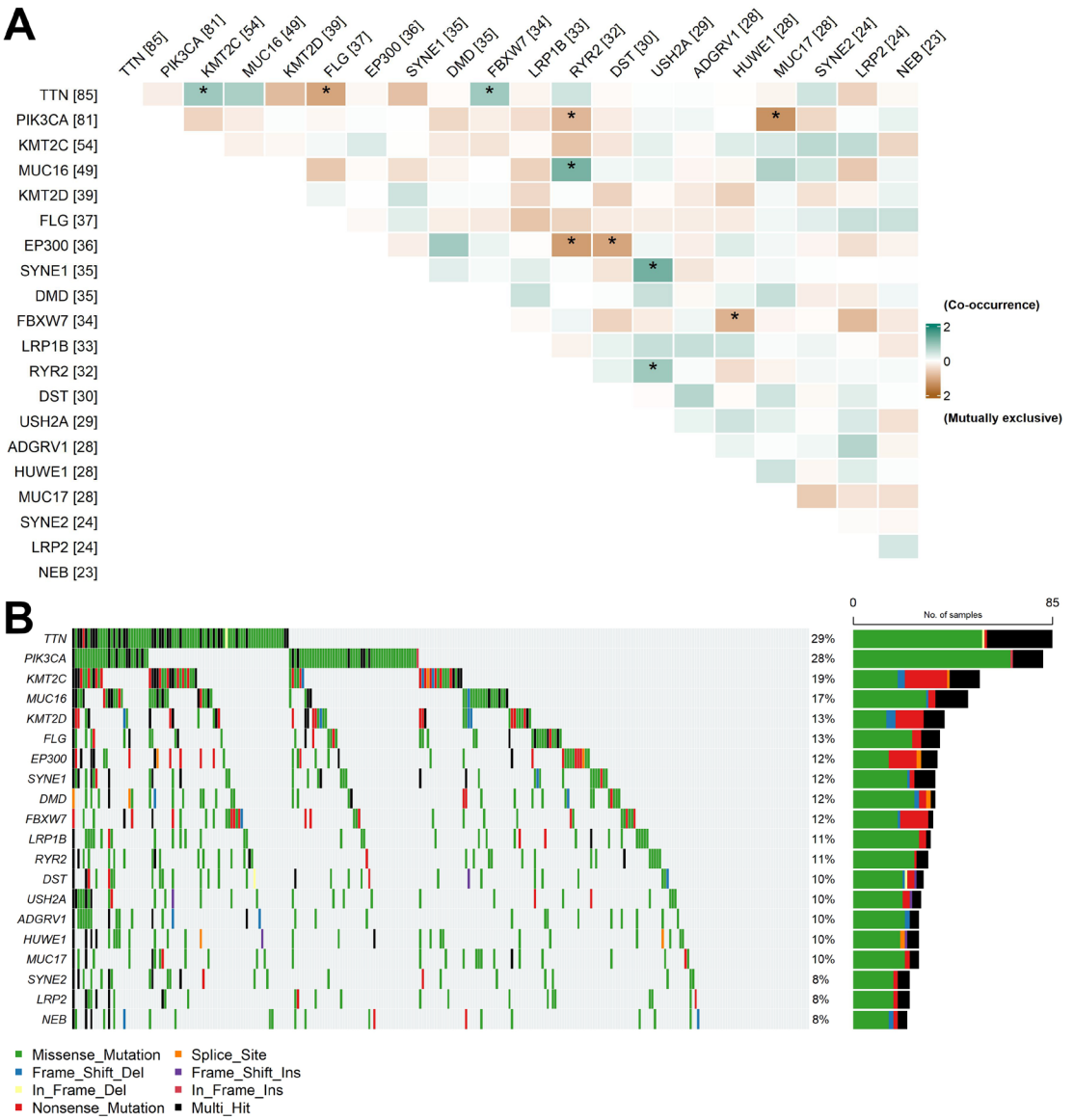

Figure 2. **(A)** Co-Mutation and Mutual Exclusivity Patterns of PIK3CA in CESC (green: co-occurrence; brown: mutual exclusivity) **(B)** Mutational Landscape of CESC.

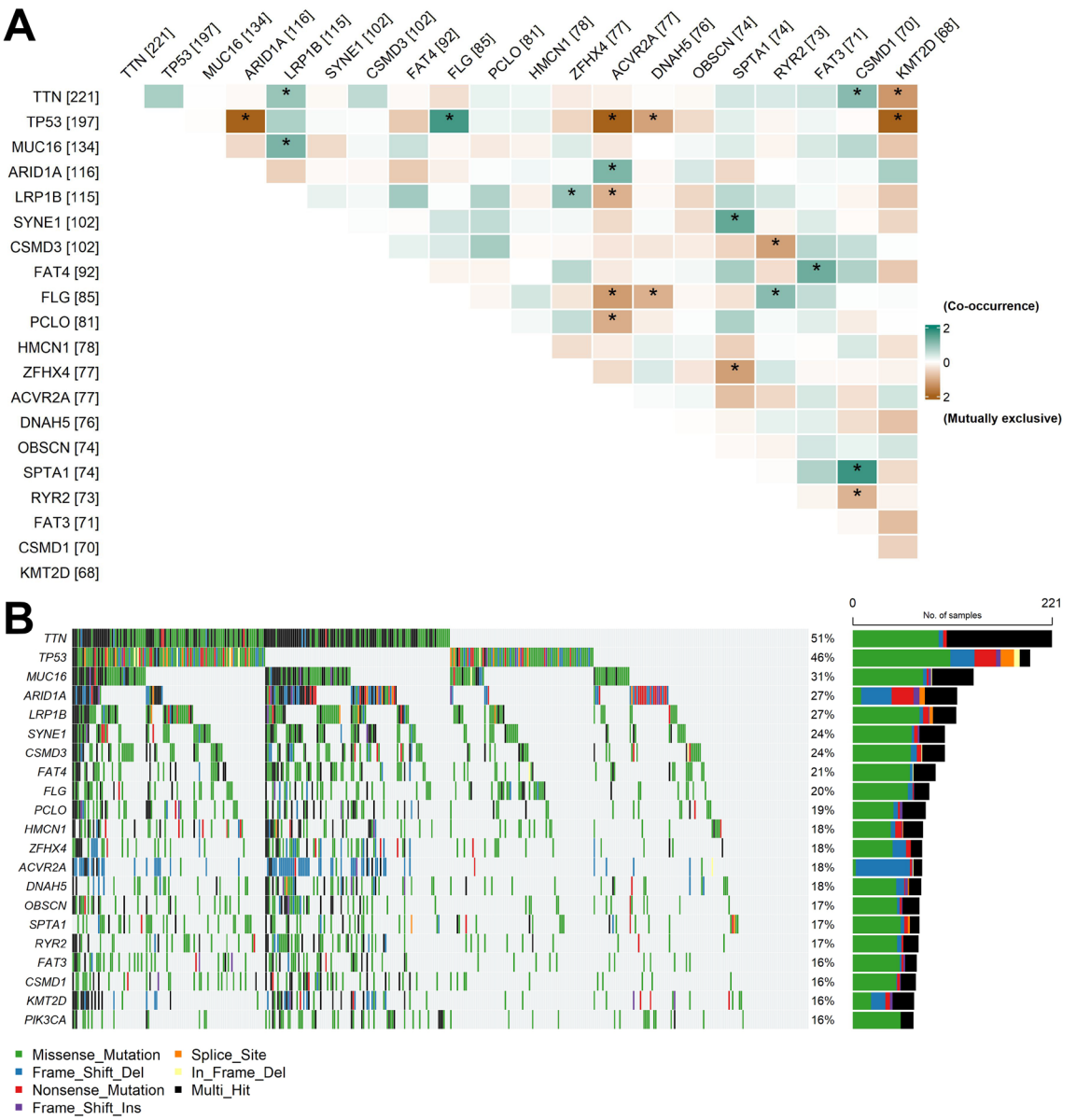

Figure 3. (A) Co-Mutation and Mutual Exclusivity Patterns of PIK3CA in STAD (green: co-occurrence; brown: mutual exclusivity) **(B)** Mutational Landscape of STAD.

exclusivity with TP53 (p = 0.001, OR = 0.36) and CSMD3 (p = 0.009, OR = 0.38) **(Figure 3A)**. Oncoprint analysis identified a distinct molecular subtype characterized by frequent PIK3CA/ARID1A co-mutations and rare TP53 alterations **(Figure 3B)**.

In LUAD, PIK3CA (5% prevalence) alterations showed a refined pattern of mutational exclusivity and co-occurrence. TMB-adjusted analysis revealed that PIK3CA maintained a robust and significant mutual exclusivity specifically with MUC17 (p = 0.037, OR = 0.11), while also demonstrating a significant co-occurrence with USH2A (p = 0.038, OR = 2.52) **(Figure 4A)**. Oncoprint analysis confirmed that PIK3CA mutations were distributed as independent events, exhibiting a pattern distinct from the mutational hotspots of TP53 or KRAS **(Figure 4B)**.

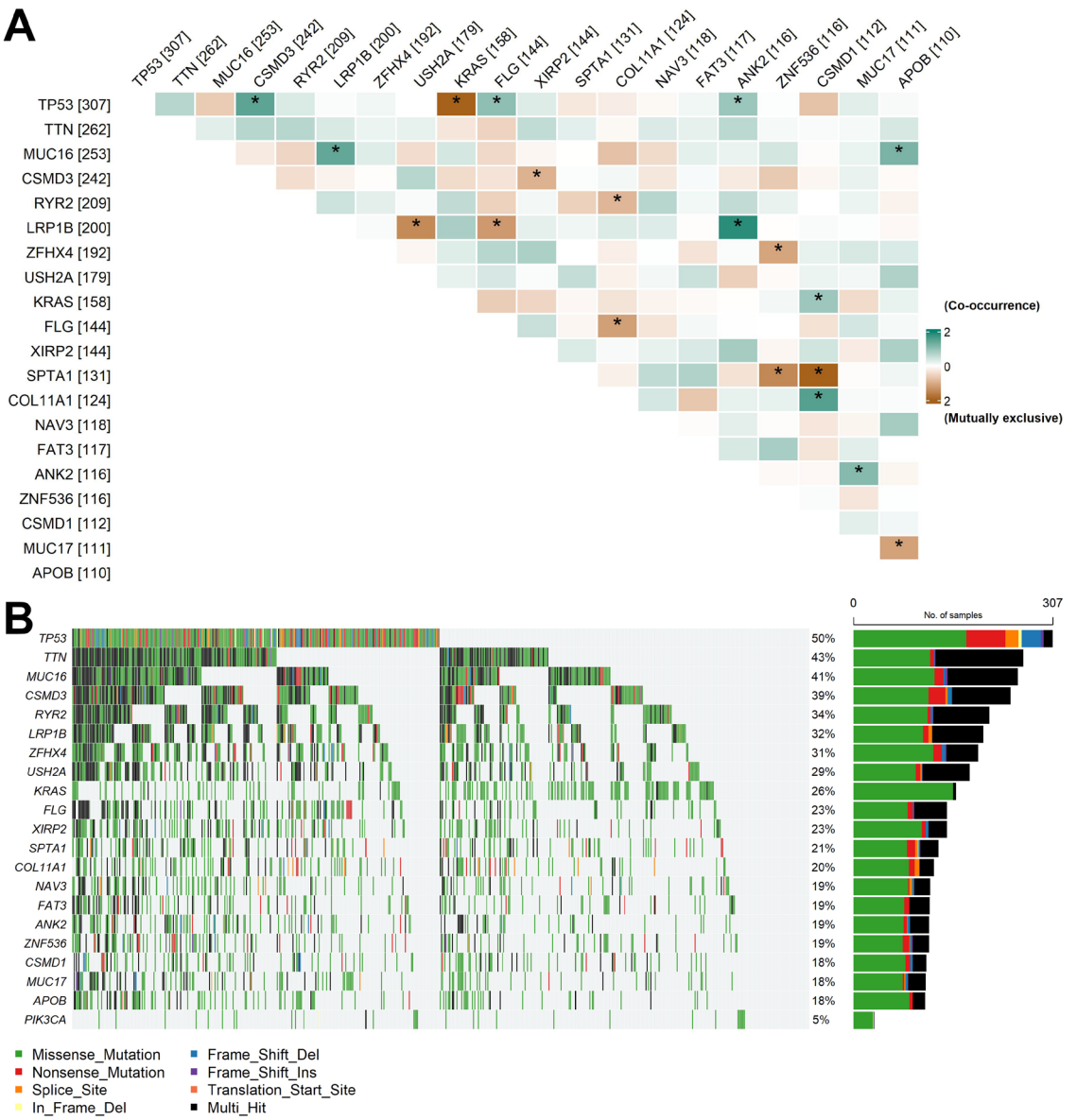

Figure 4. (A) Co-Mutation and Mutual Exclusivity Patterns of PIK3CA in LUAD (green: co-occurrence; brown: mutual exclusivity) **(B)** Mutational Landscape of LUAD.

DISCUSSION

In COAD, the PIK3CA mutational landscape is characterized by prominent co-occurrence with KRAS and strict mutual exclusivity with TP53. PIK3CA mutations (occurring in approximately 30% of samples) significantly co-occur with KRAS independently of global mutation burden. This relationship implies that concurrent activation of the PI3K/AKT and MAPK pathways is a selected evolutionary advantage in colorectal tumorigenesis, likely driving more aggressive phenotypes and contributing to broad resistance against EGFR inhibitors(13,14). Notably, the strong mutual exclusivity between PIK3CA and TP53, visualized with minimal overlap on the oncoprint, suggests that tumors in this subset follow distinct evolutionary trajectories. While TP53-mutated tumors heavily

rely on genomic instability, PIK3CA-driven tumors appear to be primarily sustained by constitutive PI3K pathway activation(6,9,15). The lack of significant correlation with APC (altered in 71% of cases) highlights that Wnt pathway dysregulation remains independent of PIK3CA-driven oncogenesis(16). Clinically, PIK3CA-mutated tumors without TP53 loss may constitute a highly specific, targetable subgroup for PI3Kα inhibitors(17). These findings underscore the necessity of integrating robust, TMB-corrected co-mutation profiles into the therapeutic stratification of colorectal cancer.

In CESC, TMB-adjusted analysis unveils a unique and highly specific mutational context for PIK3CA. PIK3CA mutations exhibited a profound mutual exclusivity with the mucin gene MUC17 and the calcium channel regulator RYR2. MUC17 is critical for maintaining epithelial barrier function, and alterations in mucins are deeply tied to tumor microenvironment interactions(18). The strong mutual exclusivity suggests that PI3K-driven cervical tumors may bypass the need for mucin-mediated microenvironmental disruption. Similarly, the exclusivity with RYR2 points towards alternative mechanisms of calcium signaling or cellular stress adaptation in PIK3CA-mutant tumors(19). Notably, PIK3CA has no significant association with TP53 or classical oncogenes in CESC, emphasizing its context-dependent role. Clinically, the mutual exclusivity with MUC17 and RYR2 may help in defining a distinct patient subgroup that could be particularly responsive to PI3K inhibitors, as these tumors lack confounding mutations in epithelial barrier or calcium regulation pathways(20).

In STAD, PIK3CA mutations exhibit a defining, true functional co-occurrence with the chromatin remodeling gene ARID1A, while maintaining mutual exclusivity with TP53 and CSMD3. The highly significant co-occurrence with ARID1A suggests a potent synergy between PI3K pathway activation and epigenetic dysregulation—a critical hallmark of gastric carcinogenesis(21). This robust interaction, sustained after rigorous TMB adjustment, implies that ARID1A loss may sensitize gastric tumor cells to PI3K dependence. Conversely, the strict mutual exclusivity with TP53 indicates that STAD tumors with PIK3CA activation can robustly progress without requiring the inactivation of p53, representing an alternative oncogenic route(22). The exclusivity with CSMD3 further separates PIK3CA-driven tumors from those relying on the dysregulation of large structural or adhesion-related tumor suppressors. Clinically, this positions PIK3CA as a central component of a distinct STAD su bgroup. These ARID1A-mutated/TP53-wild-type tumors present a unique therapeutic vulnerability, making the combination of epigenetic modulators and PI3K-targeted therapies a highly promising avenue for exploration(23).

In LUAD, the TMB-corrected co-mutation landscape of PIK3CA identifies significant interactions independent of the common mutational background typical of lung cancers. PIK3CA (altered in 5% of cases) showed a robust mutual exclusivity specifically with MUC17, mirroring the pattern observed in CESC, and a significant co-occurrence with USH2A. The mutual exclusivity with MUC17 reinforces the hypothesis that PIK3CA-mutated adenocarcinomas rely on intracellular metabolic and proliferative signals rather than structural barrier disruption(18). Furthermore, the co-occurrence with USH2A—a gene associated with cellular structural integrity—suggests potential

cross-talk between PI3K signaling and localized cytoskeletal dynamics, although the precise functional implications remain to be elucidated. Crucially, PIK3CA mutations rarely co-occur with major LUAD drivers like KRAS, reinforcing its role as an independent driver in a specific, narrow subset of tumors(24). The absence of complex confounding mutations suggests that this unique subset of PIK3CA-mutant LUADs may represent an ideal, uncluttered niche for targeted PI3K inhibitor monotherapy(25).

Limitations of the study

Although the findings of this study provide important, statistically robust insights for cancer research and personalized treatment strategies, they contain certain limitations. First, while TMB-adjusted logistic regression effectively mitigates false positives driven by global mutation burden, the biological roles and functional consequences of the observed true co-mutations (such as PIK3CA/ARID1A synergy or PIK3CA/MUC17 exclusivity) require rigorous in vitro and in vivo experimental validation to be fully confirmed. Second, because this research relies entirely on retrospective bioinformatics analyses of genomic data retrieved from the TCGA database, it lacks direct correlative data regarding patient responses to specific targeted therapies. Future studies must focus on providing functional evidence to successfully translate these identified, TMB-independent co-mutation relationships into actionable clinical applications and precision cancer therapies.

CONCLUSION

In conclusion, this study provides a comprehensive, TMB-adjusted analysis of the co-mutation landscape of PIK3CA across different cancer types, highlighting genuine molecular interactions that influence tumor progression and therapeutic responses. By integrating TCGA data with robust multivariate logistic regression, we successfully eliminated the confounding effects of background mutational noise, identifying key genetic associations—such as the synergy with KRAS in COAD and ARID1A in STAD, as well as the exclusivity with TP53 and MUC17. This refined molecular mapping offers critical insights into the evolutionary trajectories of PIK3CA-mutant tumors and provides a stringent, statistically sound framework for advancing more effective precision oncology approaches. Future studies should prioritize the functional validation of these interactions to translate these findings into improved combination therapies in the clinic.

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Conflict of Interest

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

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Ethical Declaration

This study does not contain any clinical or experimental research data obtained directly from human participants or animal subjects by the author. All data in this study were obtained from publicly available databases. The author of this article declares that the materials and methods used in their research did not require ethics committee approval and/or any special legal permission

Author Contributions

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Research Article

Attitudes toward vaccines and their relationship with health literacy among İnönü University students

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Abstract

Objective: This study aimed to determine attitudes toward vaccination among university students and to examine the relationship between these attitudes and health literacy levels.

Method: The population of this cross-sectional study consisted of students at İnönü University. The minimum sample size was calculated as 295 using PASS 11 software. Data were collected between November and December 2017 using faculty-based cluster sampling and a 47-item questionnaire. The questionnaire included items on sociodemographic characteristics, attitudes toward vaccination, and the Turkish Health Literacy Scale (THLS-32). Data were analyzed statistically, and $p<0.05$ was considered significant.

Results: A total of 335 students participated in the study (55.1% female; mean age: 21.80±3.06 years). Among the participants, 75.1% considered vaccines effective, and 67.5% identified health authorities as their primary source of vaccine-related information. The mean THLS-32 score was 32.60±9.61. Health literacy level was significantly associated with faculty group ($p=0.001$) and number of siblings ($p=0.037$), whereas no significant association was observed with gender ($p=0.127$) or income level ($p=0.837$). Health literacy was also significantly associated with several vaccine-related attitudes and beliefs, including media influence, tetanus vaccination, information sources, and thiomersal-related concerns (all $p<0.05$).

Conclusion: Although attitudes toward vaccination among university students were generally positive, media-related information had the potential to influence vaccination attitudes. Higher health literacy was associated with greater resistance to inaccurate information. Health literacy interventions may contribute to more favorable attitudes toward vaccination.

Keywords: Health literacy; universities; vaccination.

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INTRODUCTION

Immunization is defined by the World Health Organization as the process by which an individual becomes resistant to an infectious disease through vaccination or other means; vaccines protect individuals against subsequent infections by stimulating the body's own immune system (1). Vaccines represent one of the greatest achievements of biomedical science and are considered the most effective public health intervention of the twentieth century (2). Through vaccination programs, the burden of infectious diseases has been dramatically reduced, and the fear of losing children to infectious diseases has largely disappeared in developed countries (1). In the history of public health, the only intervention comparable to vaccination in terms of its impact on human health is access to safe drinking water (3).

Despite the rarity of vaccine-preventable diseases in developed countries, anti-vaccination movements and vaccine hesitancy have emerged (4). Although independent expert evaluations and the World Health Organization have repeatedly demonstrated that vaccines possess a substantially higher safety profile than therapeutic drugs, public attention has increasingly focused on vaccine safety rather than vaccine effectiveness (5). While vaccines may rarely be associated with serious acute or chronic adverse effects, current safety records strongly support that vaccination programs are both safe and effective for the vast majority of the pediatric population (6). Today, vaccines are regarded as highly safe interventions, whereas a considerable proportion of vaccine-related fears circulating in the public sphere are based on unsubstantiated claims (7).

Vaccine hesitancy has emerged as a major public health concern because it may reduce vaccination uptake and compromise the success of immunization programs worldwide. In recognition of its growing impact, the World Health Organization (WHO) listed vaccine hesitancy among the ten leading threats to global health in 2019 (8). The WHO Strategic Advisory Group of Experts (SAGE) on Immunization describes vaccine hesitancy as a context-dependent phenomenon that differs according to time, place, and vaccine type and is shaped by factors related to confidence, complacency, and convenience (9).

Health literacy is defined as "the capacity of individuals to obtain, process, and understand basic health information and services needed to make appropriate health decisions" and plays a crucial role in health promotion, disease prevention, early screening, clinical decision-making, and health policy development (10).

Within this context, the present study aimed to determine attitudes toward vaccines among students at İnönü University and to evaluate the relationship between these attitudes and health literacy levels.

METHOD

Study design and sample

This cross-sectional study was conducted among students enrolled at İnönü University. Data were collected between November and December 2017. The sample size was calculated using PASS (Power Analysis and Sample Size) version 11 software based on parameters obtained from a previously published study entitled "Healthy Lifestyle Behaviors and Associated Factors Among Students of Fırat

University Elazığ School of Health." The minimum required sample size was determined to be 295 participants to achieve 80% statistical power with a 95% confidence level. A cluster sampling method based on faculty groups was employed to create clusters of equal or nearly equal size. At the completion of the study, a total of 335 participants had been recruited, thereby exceeding the minimum required sample size.

Data collection instruments

Data were collected using a 47-item questionnaire consisting of three sections. The first section included sociodemographic characteristics (sex, age, faculty, monthly family income, and number of siblings). The second section assessed attitudes toward vaccines. The third section evaluated participants' health literacy levels using the Turkish Health Literacy Scale (THLS-32).

The THLS-32 is the Turkish adaptation of the European Health Literacy Survey Questionnaire developed by the European Health Literacy Survey Consortium (HLS-EU Consortium, 2012). The scale was designed to assess health literacy among individuals aged 15 years and older and is based on a 12-dimensional conceptual framework comprising three health domains (health care, disease prevention, and health promotion) and four information-processing competencies (accessing, understanding, appraising, and applying health information).

Each of the 32 items is rated on a four-point Likert scale ranging from "very difficult" (1) to "very easy" (4), while the response "I do not know" is coded as 5. For scoring purposes, responses are reverse-coded from 1–4 to 4–1. To facilitate interpretation, the overall score is standardized to a scale ranging from 0 to 50 using the following formula: Index = (Mean − 1) × (50 / 3)

A score of 0 represents the lowest level of health literacy, whereas a score of 50 represents the highest level. Total scores are categorized into four levels: inadequate (0–25), problematic/limited (>25–33), adequate (>33–42), and excellent (>42–50) health literacy. The validity and reliability study of the Turkish version was conducted by Okyay and Abacıgil in May 2016, and the internal consistency coefficient was reported as 0.982 (11).

Statistical analysis

Statistical analyses were performed using SPSS (Statistical Package for the Social Sciences) version 17. Statistical significance was accepted at $p<0.05$. The normality of data distribution was assessed using the Kolmogorov–Smirnov and Shapiro–Wilk tests.

For normally distributed continuous variables, comparisons between two independent groups were performed using Student's t-test, whereas comparisons among more than two groups were conducted using one-way analysis of variance (ANOVA). For non-normally distributed continuous variables, the Mann–Whitney U test and Kruskal–Wallis test were used. Associations between categorical variables were evaluated using Pearson's chi-square test. When cells with expected frequencies below five exceeded 25% of all cells, the Monte Carlo corrected chi-square test was applied.

Missing data were handled using an available-case analysis. Participants with missing responses for a variable were excluded only from analyses involving that particular variable. Therefore, the number of participants included in individual analyses varied slightly according to data completeness. No missing-value imputation was performed.

Ethical approval

Ethical approval was obtained from the Ethics Committee of İnönü University (Decision No 2017/25-11) before the initiation of the study. Additional administrative approval was obtained from the Rectorate of İnönü University. Verbal informed consent was obtained from all participants prior to questionnaire administration. Participants were informed that their responses would remain confidential and that participation was entirely voluntary.

RESULTS

A total of 335 students were included in the study. Because of item-level missing responses, the number of participants included in individual analyses varied according to the variables examined. Of the participants, 184 (55.1%) were female and 150 (44.9%) were male, with a mean age of 21.80 ± 3.06 years. Monthly family income was at or below the hunger threshold in 85 participants (25.6%), between the hunger and poverty thresholds in 172 participants (51.8%), and at or above the poverty threshold in 75 participants (22.6%). Regarding the number of siblings, most participants reported having 1–3 siblings (n=165, 49.5%) or 4–6 siblings (n=120, 36.0%), whereas 20 participants (6.0%) had no siblings and 28 (8.4%) had seven or more siblings. The distribution of participants according to faculty and other sociodemographic characteristics is presented in **Table 1.**

Table 1. Sociodemographic characteristics of the study population (n = 335)

Variable	n	%
Sex		
Male	150	44.9
Female	184	55.1
Faculty groups		
Social Sciences	137	40.9
Natural Sciences	77	23.0
Health Sciences	121	36.1
Income distribution (TL)		
At or below the **hunger** threshold*	85	25.6
Between the hunger and poverty thresholds*	172	51.8
At or above the **poverty** threshold*	75	22.6
Number of siblings		
None	20	6.0
1–3 siblings	165	49.5
4–6 siblings	120	36.0
≥7 siblings	28	8.4
Age, mean ± SD (years)	21.80 ± 3.06	

Abbreviations: n, number of participants; SD, standard deviation; %, percentage.
Note: Income groups were classified according to the nationally defined hunger and poverty threshold criteria in Türkiye during the study period.

When participants were asked to identify vaccines routinely administered within the national immunization program in Türkiye, the highest recognition rates were observed for the measles–mumps–rubella (MMR) vaccine (81.5%) and varicella vaccine (73.4%). More than half of the participants were also aware of the hepatitis B vaccine (69.9%) and tetanus vaccine (64.2%). In contrast, awareness of the human papilloma virus (HPV) vaccine (5.7%), rotavirus vaccine (14.0%), conjugate pneumococcal vaccine (18.5%), and influenza vaccine (31.3%) was relatively low.

In response to the question, "Do you think vaccines are effective?", 251 participants (75.1%) reported that vaccines were effective, 69 (20.7%) considered them partially effective, four (1.2%) considered them ineffective, and ten (3.0%) stated that they had no opinion. Regarding the question, "Do you think vaccines have side effects?", 218 participants (65.1%) answered "yes," 38 (11.3%) answered "no," and 79 (23.6%) reported having no opinion.

Table 2. Distribution of health literacy categories according to sex

Sex	Inadequate n	%	Problematic/ Limited n	%	Adequate n	%	Excellent n	%	Total n	%
Male	35	10.6	44	13.3	45	13.6	24	7.3	148	44.8
Female	32	9.7	59	17.9	56	17.0	35	10.6	182	55.2
Total	67	20.3	103	31.2	101	30.6	59	17.9	330	100.0

Pearson's Chi-square test was used ($\chi^2 = 2.087$, p = 0.555).

Abbreviations: n, number of participants; %, percentage.

For the question concerning perceived vaccine side effects, fever (66.3%), nausea (54.9%), headache (45.7%), and vomiting (41.2%) were the most frequently reported responses. In contrast, autism (3.9%), multiple sclerosis (6.3%), and subacute sclerosing panencephalitis (7.8%) were reported at considerably lower frequencies.

Health authorities were identified as the primary source of vaccine-related information by 67.5% of participants, followed by the media (16.7%), people in their social environment (13.7%), and politicians (1.5%). Furthermore, 156 participants (46.6%) reported that media coverage regarding vaccine side effects could influence their opinions about vaccines. When asked whether they would receive the annual influenza vaccine if recommended by health authorities, 118 participants (35.2%) responded affirmatively, whereas 181 (54.0%) stated that they would not receive the vaccine.

The mean THLS-32 score was 32.60 ± 9.61. Based on the predefined categories, 67 participants (20.3%) were classified as having inadequate health literacy, 103 (31.2%) as limited health literacy, 101 (30.6%) as adequate health literacy, and 59 (17.9%) as excellent health literacy. The distribution of health literacy categories according to sex is presented in **Table 2**. No statistically significant difference was observed between males and females (χ^2=2.087, p=0.555).

The distribution of THLS-32 scores according to descriptive characteristics is summarized in **Table 3**. Although the mean score was higher among females (33.40 ± 9.22) than males (31.78 ± 10.12), the difference was not statistically significant (p=0.127). According to faculty

Table 3. Distribution of THLS-32 mean scores according to descriptive variables

Variable	n	Mean ± SD	p-value
Health literacy (overall)	331	32.60 ± 9.61	—
Sex			
Male	148	31.78 ± 10.12	0.127
Female	178	33.40 ± 9.22	
Faculty groups			
Social Sciences	133	30.45 ± 9.56	0.001
Natural Sciences	73	31.47 ± 9.98	
Health Sciences	120	35.85 ± 8.76	
Income distribution (TL)			
At or below the hunger threshold*	85	32.45 ± 9.77	0.837
Between the hunger and poverty thresholds*	167	32.99 ± 9.86	
At or above the poverty threshold*	74	32.17 ± 9.16	
Number of siblings			
None	20	34.34 ± 13.80	0.037
1–3 siblings	163	33.77 ± 9.46	
4–6 siblings	116	31.74 ± 8.68	
≥7 siblings	27	28.68 ± 10.27	

Abbreviations: n, number of participants; SD, standard deviation.
Note: Independent samples t-test was used for comparisons between two groups, and one-way analysis of variance (ANOVA) was used for comparisons among more than two groups. $p < 0.05$ was considered statistically significant.
*Income groups were classified according to the nationally defined hunger and poverty threshold criteria in Türkiye during the study period.

Table 4. Distribution of responses to the question "Would you receive a tetanus vaccine if you had an actively bleeding wound?" according to health literacy categories

Response	Inadequate n	%	Problematic/ Limited n	%	Adequate n	%	Excellent n	%	Total n	%
Yes	22	6.7	40	12.1	60	18.2	39	11.8	161	48.8
No	20	6.1	43	13.0	29	8.8	16	4.8	108	32.7
No opinion	25	7.6	20	6.1	12	3.6	4	1.2	61	18.5
Total	67	20.3	103	31.2	101	30.6	59	17.9	330	100.0

Pearson's Chi-square test was used ($\chi^2 = 34.994$, $p = 0.001$). Abbreviations: n, number of participants; %, percentage.

groups, health sciences students demonstrated significantly higher mean scores (35.85 ± 8.76) than students from the natural sciences (31.47 ± 9.98) and social sciences (30.45 ± 9.56) faculties (p=0.001). Evaluation according to the number of siblings revealed mean scores of 34.34 ± 13.80 among participants without siblings, 33.77 ± 9.46 among those with 1–3 siblings, 31.74 ± 8.68 among those with 4–6 siblings, and 28.68 ± 10.27 among those with seven or more siblings. This difference was statistically significant (p=0.037). No significant differences in mean scores were observed across monthly income categories (p=0.837).

A statistically significant association was found between health literacy level and responses to the question, "Would you receive a tetanus vaccine if you had an actively bleeding wound?" **(Table 4; χ^2=34.994, p=0.001)**. In contrast, no significant association was observed between health literacy categories and responses to the question regarding whether vaccines have side effects (p=0.221).

A significant relationship was identified between health literacy levels and responses to the question, "Could media reports about the side effects of a vaccine change your opinion about vaccines?" **(Table 5; χ^2=18.140, p=0.006).** Similarly, a statistically significant association was observed between health literacy levels and responses to the question, "What is the primary source that shapes your opinion about vaccines?" **(Table 6; χ^2=12.807, p=0.046).** However, no significant association was found between health literacy levels and responses to the question, "Would you receive the annual influenza vaccine even if it were recommended by health authorities?" (p=0.808).

Responses to the question, "Would the presence of trace amounts of thiomersal (a mercury-containing compound) in vaccines prevent you

Table 5. Distribution of responses to the question "Could a media report about the side effects of a vaccine change your opinion about vaccination?" according to health literacy categories

Response	Inadequate n	%	Problematic/ Limited n	%	Adequate n	%	Excellent n	%	Total n	%
Yes	33	10.0	53	16.0	47	14.2	22	6.6	155	46.8
No	17	5.1	24	7.3	44	13.3	23	6.9	108	32.6
No opinion	17	5.1	27	8.2	10	3.0	14	4.2	68	20.5
Total	**67**	**20.2**	**104**	**31.4**	**101**	**30.5**	**59**	**17.8**	**331**	**100.0**

Pearson's Chi-square test was used ($\chi^2 = 18.140$, $p = 0.006$).

Abbreviations: n, number of participants; %, percentage.

Table 6. Distribution of responses to the question "What is the primary source that shapes your opinion about vaccines?" according to health literacy categories

Source	Inadequate n	%	Problematic/ Limited n	%	Adequate n	%	Excellent n	%	Total n	%
Media / politicians	14	4.2	14	4.2	23	7.0	8	2.4	59	17.9
Health authorities	37	11.2	76	23.0	66	20.0	47	14.2	226	68.5
People around them	15	4.5	14	4.2	12	3.6	4	1.2	45	13.6
Total	66	20.0	104	31.5	101	30.6	59	17.9	330	100.0

Pearson's Chi-square test was used ($\chi^2 = 12.807$, $p = 0.046$).

Abbreviations: n, number of participants; %, percentage.

Table 7. Distribution of responses to the question "Would the presence of trace amounts of thiomersal (a mercury-containing compound) in vaccines prevent you from being vaccinated?" according to health literacy categories

Thiomersal	Inadequate n	%	Problematic/ Limited n	%	Adequate n	%	Excellent n	%	Total n	%
No, it would not prevent vaccination	9	2.7	20	6.0	35	10.6	18	5.4	82	24.8
Yes, it would prevent vaccination	30	9.1	52	15.7	31	9.4	21	6.3	134	40.5
No opinion	28	8.5	32	9.7	35	10.6	20	6.0	115	34.7
Total	67	20.2	104	31.4	101	30.5	59	17.8	331	100.0

Pearson's Chi-square test was used ($\chi^2 = 16.345$, $p = 0.012$).

Abbreviations: n, number of participants; %, percentage

from being vaccinated?" differed significantly according to health literacy level (**Table 7; χ^2=16.345, p=0.012**).

DISCUSSION

The findings of the present study indicate that attitudes toward vaccines among university students were generally positive. However, media-derived information appeared to have a substantial potential to influence vaccine-related attitudes, whereas higher levels of health literacy seemed to exert a protective effect against inaccurate and biased information.

A similar study conducted in Poland involving 1,320 university students reported fever (38%), redness or swelling (28%), and allergic reactions (18%) as the most frequently recognized vaccine-related adverse effects (12). Consistent with these findings, fever was identified as the most widely recognized vaccine side effect in the present study. In contrast, awareness of chronic complications allegedly associated with vaccination was considerably lower. This finding may reflect a lack of public knowledge regarding chronic vaccine-related complications. Such knowledge gaps may create a context in which individuals become more susceptible to biased information, thereby influencing attitudes toward vaccination.

Several studies examining the relationship between sex and health literacy have reported significantly higher health literacy levels among

women. Evidence supporting this observation has been reported among patients with diabetes in a study published in JAMA (13), among older adults in China (14), and among adolescent and young adult populations (15,16). Although female participants in the present study demonstrated higher mean THLS-32 scores than males, the difference did not reach statistical significance (p=0.127). Nevertheless, this finding appears to be directionally consistent with the existing literature and may represent a trend that could achieve statistical significance in studies with larger sample sizes. Therefore, male university students may represent a priority target group for interventions aimed at improving health literacy.

Previous studies conducted in the United States (17) and among older adults in China (18) have reported significant positive associations between monthly income and health literacy. No such association was observed in the present study (p=0.837). This discrepancy may be attributable to the relatively homogeneous nature of the study population, consisting exclusively of university students at similar educational stages. In such a population, health-related interests and competencies may be less influenced by family income. Notably, the significant differences observed between faculty groups (p=0.001) are consistent with findings from a Chinese study comparing engineering students with medical and health sciences students (19), supporting the notion that health sciences students possess inherently higher levels of health literacy. This finding suggests that interventions designed to improve health literacy should particularly target students enrolled in non-health-related disciplines.

The observed increase in health literacy scores with decreasing numbers of siblings (p=0.037) is consistent with findings from a meta-analysis reporting an inverse relationship between family size and health literacy (20). One possible explanation is that smaller family size may be associated with higher parental educational attainment. Since higher parental education levels have been linked to lower fertility rates, this indirect pathway may help explain the relationship between sibling number and health literacy.

A previous study examining sources of information used in vaccine-related decision-making reported healthcare professionals (81.7%) as the most influential source, followed by family members (47.3%), other families (23.0%), friends (22.5%), and the internet (9.9%) (21). In the present study, health authorities remained the predominant source of information (67.5%), although the media also occupied a relatively influential position (16.7%). This difference may be attributable to the younger age profile of the study population and their greater exposure to social media. More importantly, the preferred source of vaccine-related information was significantly associated with health literacy categories (p=0.046). The increasing reliance on health authorities with higher levels of health literacy suggests that health literacy influences not only the interpretation of information but also the selection of information sources. Similarly, Ashkenazi et al. reported that parents who relied primarily on healthcare professionals demonstrated greater vaccine knowledge and lower vaccine hesitancy than those obtaining information from informal or internet-based sources, emphasizing the importance of reliable information sources in vaccination decision-making (22).

Regarding the influence of media on vaccine attitudes, a review conducted in the United States reported that approximately 11% of local evening news coverage consisted of health-related news, much of which was characterized as biased or lacking appropriate context, thereby undermining public confidence in vaccines (23). In the present study, 46.6% of participants reported that media reports concerning vaccine side effects could alter their opinions about vaccines, demonstrating a structural similarity to these international findings. Furthermore, a significant association was observed between responses to this question and health literacy levels (p=0.006). This finding suggests that interventions aimed at improving health literacy may enhance resilience against biased vaccine-related information disseminated through the media. This interpretation is supported by Wilson and Wiysonge, who highlighted the growing influence of social media in spreading vaccine misinformation and undermining public confidence in vaccination programmes (24).

To date, no large-scale case-control or cohort study has confirmed the hypothesized association between thiomersal and the development of autism spectrum disorder (ASD). Since 1999, the global use of thiomersal-containing vaccines has steadily declined, whereas the prevalence of ASD has continued to increase, providing evidence against a causal relationship. Moreover, no contraindications have been reported for the use of thiomersal-containing vaccines in infants, children, or non-pregnant women. The risks associated with vaccine-preventable diseases and their complications substantially outweigh any potential risks related to immunization with thiomersal-containing vaccines (25). Despite this substantial body of evidence, 40.3% of participants reported that the presence of thiomersal could influence their vaccination decisions, indicating that scientifically refuted claims continue to exert influence at the societal level. Furthermore, a significant association was identified between health literacy and attitudes toward thiomersal-containing vaccines (p=0.012). Higher health literacy levels were associated with more accurate knowledge regarding thiomersal and with less negative attitudes toward vaccination. This interpretation is supported by recent evidence indicating that higher levels of health literacy are associated with lower vaccine hesitancy, whereas limited health literacy may increase susceptibility to misinformation and negative attitudes toward vaccination (26). Therefore, initiatives aimed at improving health literacy may help counter vaccine-related misconceptions and should be encouraged.

Limitations of the study

Several limitations of the present study should be acknowledged. First, the study population consisted exclusively of university students, the majority of whom had not yet become parents. Therefore, further research focusing specifically on parents of reproductive age is warranted. The single-center and cross-sectional design may limit the generalizability of the findings. Data collection was completed in late 2017, prior to the COVID-19 pandemic. Given the profound impact of the pandemic on public perceptions of vaccination, attitudes toward vaccines may have changed substantially in subsequent years. Therefore, the findings should be interpreted within the temporal context in which the study was conducted.

CONCLUSION

The findings of the present study demonstrated variability in attitudes toward vaccination among university students. The majority of participants regarded vaccines as an effective preventive public health intervention. However, media content was also found to influence perceptions and attitudes toward vaccines. Therefore, increasing the visibility of scientific and trustworthy health authorities in the media and preventing the dissemination of inaccurate or incomplete information may be important for reducing the negative impact of misleading or biased publications on public opinion.

The results further indicated that higher levels of health literacy were associated with greater resistance to misinformation related to health. Individuals with higher health literacy appeared to be more capable of distinguishing reliable and accurate information from misleading or inaccurate claims. In this context, health literacy not only empowers individuals in making informed health decisions but also serves a protective role against anti-vaccination messages and misleading content. Expanding initiatives aimed at improving health literacy across the population may contribute to the development of more positive attitudes toward vaccination among future generations.

Despite exposure to negative information and publications, confidence in vaccines was found to remain generally high among participants. The implementation of comprehensive vaccine communication programs may therefore be essential for maintaining public trust in vaccination and preserving its societal value. Furthermore, scientific evidence should remain the primary basis for decision-making in matters directly affecting public health, such as vaccination, and policies should be aligned with recommendations from health authorities. Vaccination should be regarded as a fundamental public health practice and evaluated independently of political debates.

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Research Article

Evaluation of patients who underwent invasive mechanical ventilation in a pediatric intensive care unit: A prospective study

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Abstract

Objective: To evaluate the use of invasive mechanical ventilation (MV) during a one-year period (2015–2016) in a pediatric intensive care unit (PICU), identify the most common complications and mortality rates, and compare study-period practices with more recent evidence to characterize changes in pediatric MV management over the past decade.

Method: Among 781 patients followed in the PICU of Çukurova University Faculty of Medicine between February 2015 and February 2016, 173 patients who underwent invasive MV were prospectively included. Demographic data, primary diagnoses, MV indications, PICU severity scores (Pediatric Index of Mortality [PIM II], Pediatric Risk of Mortality [PRISM III], and Pediatric Logistic Organ Dysfunction [PELOD]), ventilation modes and parameters, tracheostomy status, sedation-analgesia use, weaning, complications, and ventilator-associated pneumonia (VAP) rates were analyzed.

Result: Patient ages ranged from 2 months to 18 years (median 42 months, min-max 2-216); 57.2% were male. MV incidence was 22.1%. Neurological disease was the most common underlying condition (44.5%). Median PICU stay was 7 days (min-max 1-65) and median MV duration was 5 days (min-max 1-61). Complications occurred in 20.2% of patients; atelectasis (7.5%), VAP (6.9%), and pneumothorax (5.2%) were most frequent. VAP rate was 4.46/1,000 ventilator days. Tracheostomy was performed in 37 patients (21.4%). Mortality rate was 11%.

Conclusion: MV practices in the PICU were largely consistent with international standards. Ventilator parameters were broadly maintained within lung-protective ranges across the cohort; together with a VAP prevention bundle, this may have contributed to the comparatively low complication rate. Multicenter prospective studies are required to generate robust national data on pediatric MV practices in Turkey.

Keywords: Mechanical ventilation, indications, complications, pediatric parameters, pediatric intensive care, tracheostomy

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INTRODUCTION

Mechanical ventilation (MV) is defined as the process of maintaining respiratory function with the assistance of a device to prevent lung collapse, ensure adequate ventilation, and maintain appropriate oxygenation until the underlying pathology causing respiratory or oxygenation insufficiency is resolved. The primary objective of MV is to correct and sustain homeostasis in oxygen–carbon dioxide exchange and acid–base balance in patients with respiratory insufficiency, circulatory failure, or respiratory suppression due to central nervous system disorders (1).

Mechanical ventilation can be performed invasively or non-invasively. To provide optimal respiratory support, volume, pressure, and flow parameters must be individually tailored to each patient (2). In recent years, MV has become one of the most frequently applied life-sustaining interventions in pediatric intensive care units (PICUs), with studies reporting that more than 20% of PICU patients require invasive ventilatory support (3). With the widespread use of MV and accumulating evidence, it is now well-established that positive-pressure ventilation is not a benign process; ventilator-induced lung injury (VILI), arising from mechanisms such as volutrauma, barotrauma, atelectrauma, and biotrauma, remains a significant concern (4,5). Additional complications include pneumothorax, atelectasis, ventilator-associated pneumonia (VAP), subglottic stenosis, and oxygen toxicity.

In parallel with these developments, the approach to MV in pediatric critical care has evolved considerably. The Pediatric Mechanical Ventilation Consensus Conference (PEMVECC) has provided an internationally endorsed framework of recommendations aimed at harmonizing ventilation practices and reducing complications in critically ill children (6). Furthermore, the growing use of non-invasive modalities—particularly high-flow nasal cannula (HFNC) and bi-level positive airway pressure (BiPAP)—has increasingly deferred or averted the need for invasive MV in pediatric patients with acute respiratory failure (7).

The aim of this study was to evaluate the use of invasive MV in a tertiary PICU during a prospective one-year period (2015–2016), identify the most common complications and mortality rates, and compare these study-period practices and outcomes with more recent evidence to characterize how pediatric MV management has evolved over the past decade.

METHOD

Among 781 patients followed in the PICU of Çukurova University Faculty of Medicine between February 2015 and February 2016, 173 patients who underwent invasive MV were prospectively included in the study. Only the first MV episodes of patients with repeated applications were included. The study protocol was approved by the Ethics Committee of Çukurova University Faculty of Medicine.

During daily follow-ups, patient observation forms and medical records were reviewed to collect and record the following data: demographic information, primary diagnoses, indications for invasive MV, pediatric intensive care severity scores (Pediatric Index of Mortality [PIM II], Pediatric Risk of Mortality [PRISM III], and Pediatric Logistic Organ Dysfunction [PELOD]), type and method of ventilation, endotracheal tube or tracheostomy status, duration of PICU stay and intubation, sedation-analgesia and neuromuscular blocker use, weaning and extubation methods, complications, VAP rates,

and other outcomes. Pediatric intensive care scores were calculated using a computer-based system according to the original methodology, based on the worst physiological values recorded at PICU admission and within the first 24 hours, in line with the standard scoring windows for these instruments. Mechanical ventilator parameters were recorded daily; minimum and maximum values were used during the evaluation.

Ventilator weaning protocol

Patients were evaluated on daily clinical rounds three times per day. Blood gas analysis was performed 1–2 times daily to guide ventilator adjustments. Sedation was interrupted daily to allow clinical reassessment. Peak inspiratory pressure (PIP) and positive end-expiratory pressure (PEEP) were kept within protective limits and were not routinely escalated beyond these thresholds; weaning was achieved through stepwise reduction of pressure support as respiratory mechanics and gas exchange allowed. A spontaneous breathing trial was performed as part of extubation readiness assessment, and the decision to extubate was made at the end of clinical rounds based on the patient's respiratory status, oxygenation, and ventilator requirements.

The diagnosis of VAP was confirmed at least 48 hours after initiation of MV, based on the appearance of new progressive infiltrates on chest radiography, along with at least two of the following criteria: hyperthermia (>38°C) or hypothermia (<36°C), leukocytosis (>12,000/mm³) or leukopenia (<4,000/mm³), purulent tracheal secretions, hypoxemia (≥15% decrease in the ratio of partial pressure of arterial oxygen to fraction of inspired oxygen [PaO_2/FiO_2]), increased oxygen requirement, or increased ventilation requirement (3). All VAP diagnoses were confirmed by the hospital's infectious diseases committee. The VAP prevention bundle applied in this unit included daily weaning assessments, hand hygiene, head-of-bed elevation to 30°–45°, aseptic suctioning technique, use of closed-system suctioning, and adherence to oral care recommendations.

Statistical analysis

Data were analyzed using IBM SPSS Statistics version 20.0. Normality of distribution for continuous variables was assessed using the Shapiro-Wilk test. As age, MV duration, PICU length of stay, PIM II, PRISM III, and PELOD were not normally distributed and markedly right-skewed (Shapiro-Wilk $p<0.001$ for all), the Mann-Whitney U test was used for two-group comparisons of these variables, and they are reported as median (min-max) rather than mean ± standard deviation (SD) throughout the manuscript. The chi-square test, or Fisher's exact test when expected cell counts were <5, was used to compare categorical variables such as mortality, sex, MV indication, and primary disease. A p-value of <0.05 was considered statistically significant. To assess the association between PICU severity scores and mortality, PIM II, PRISM III, and PELOD were each entered as continuous predictors in separate univariable logistic regression models with in-hospital mortality as the outcome; results are reported as odds ratios (OR) with 95% confidence intervals (CI) and p-values. A multivariable model was not fitted given the limited number of mortality events (n=19); these findings are hypothesis-generating.

RESULTS

Patient characteristics

A total of 173 patients requiring invasive MV between February 2015 and February 2016 were prospectively analyzed. Patient ages ranged

from 2 months to 18 years (median 42 months, min-max 2-216); 99 (57.2%) were male and 74 (42.8%) were female. The incidence of MV in the study PICU was 22.1%. Neurological disease was the most common underlying condition (n=77, 44.5%), followed by metabolic disease (n=21, 12.1%), congenital cardiovascular disease (n=20, 11.5%), and oncological disease (n=11, 6.3%). The most frequent indication for MV was hypoxemic respiratory failure (n=88, 51%), followed by postoperative care (n=36, 20%), hypercapnic respiratory failure (n=20, 11%), Glasgow Coma Scale ≤8 (n=19, 11%), and shock (n=10, 6%) (**Table 1**).

Severity scores at admission ranged as follows: PIM II median 24.3% (4.5–100%), PRISM III median 20 (5–67), and PELOD median 1.3% (0.1–100%). In patients who died, the requirement for multiple inotropic agents was significantly more frequent and strongly associated with mortality. Among non-survivors, median PIM II was 100, median PRISM III was 45, and median PELOD was 76%. Each one-unit increase in PIM II was associated with a 1.11-fold increase in mortality risk (OR 1.11, 95% CI: 1.053–1.167, p<0.001); each one-unit increase in PRISM III increased mortality risk by 1.19-fold (OR 1.19, 95% CI: 1.114–1.275, p<0.001); and each one-unit increase in PELOD was associated with a 1.04-fold increase in mortality risk (OR 1.04, 95% CI: 1.026–1.062, p<0.001). No statistically significant difference was found between sexes in their effect on mortality.

Among patients on MV, the most commonly used device was the Dräger Evita-2, used in 91 patients (52.6%). Pressure-controlled ventilation was utilized in all patients; the predominant mode was synchronized intermittent mandatory ventilation with pressure support (SIMV+PS).

Table 1. Epidemiological and demographic characteristics of the cases

Variable	N	%
Age (months)		
Median (min-max)	42(2-216)	
Gender		
Female	74	42.8
Male	99	57.2
Underlying Condition		
Congenital cardiovascular diseases	20	11.5
Neurological diseases	77	44.5
Metabolic diseases	21	12.1
Oncological diseases	11	6.3
Infectious diseases	5	2.9
Nephrological diseases	11	6.3
Immunological diseases	2	1.1
Other	26	15.0
Indication for MV		
Hypoxemic respiratory failure	88	51.0
Hypercapnic respiratory failure	20	11.0
Postoperative care	36	20.0
Glasgow Coma Scale ≤8	19	11.0
Shock	10	6.0
Incidence of MV	173	22.1
Mortality	19	11.0

MV: Mechanical ventilation

Endotracheal tubes were cuffed in 110 patients (63.6%) and uncuffed in 63 patients (36.4%). The median PICU length of stay was 7 days (min-max 1-65) and median MV duration was 5 days (min-max 1-61) **(Table 2)**.

Sedation and vasoactive support

Sedation and analgesia were administered to 126 patients (72.8%). Benzodiazepines and opioids were the first-line agents; midazolam and fentanyl were the most commonly used drugs. Vasoactive or inotropic support was required in 55 patients (31.8%). The most commonly

Table 2. Pediatric Intensive Care Unit and mechanical ventilation parameters

Parameter	Mean ± SD	Median (Min-Max)
Max PIP (cmH_2O)	22.95 ± 5.25	22 (11-44)
Min PIP (cmH_2O)	18.18 ± 3.10	18 (10-28)
Max PEEP (cmH_2O)	6.28 ± 1.54	6 (5-13)
Min PEEP (cmH_2O)	5.41 ± 0.75	5 (4-9)
Max MAP (cmH_2O)	10.20 ± 1.90	9 (8-20)
Min MAP (cmH_2O)	8.45 ± 1.07	8 (7-17)
Max RR (breaths/min)	25.60 ± 6.20	25 (12-45)
Min RR (breaths/min)	19.57 ± 5.10	20 (10-35)
Max TV/kg (mL/kg)	8.16 ± 1.15	8 (6-12)
Min TV/kg (mL/kg)	6.83 ± 0.81	7 (6-10)
Max FiO_2 (%)	55.75 ± 14.30	60 (33-100)
Min FiO_2 (%)	38.39 ± 4.88	40 (30-65)
Max Ti (s)	0.92 ± 0.69	0.8 (0.7-0.9)
Min Ti (s)	0.81 ± 0.49	0.8 (0.6-0.7)
Max Trigger	1.20 ± 0.47	1.0 (0.7-2.0)
Min Trigger	1.20 ± 0.45	1.0 (0.6-2.0)
Max PS (cmH_2O)	8.65 ± 3.30	8 (5-19)
Min PS (cmH_2O)	6.31 ± 4.10	6 (0-19)
PICU LOS (days)	—	7 (1-65)
MV duration (days)	—	5 (1-61)
PIM II score	—	24.3 (4.5-100)
PRISM III score	—	20 (5-67)
PELOD score	—	1.3 (0.1-100)

SD: Standard deviation; PIP: Peak inspiratory pressure; PEEP: Positive end-expiratory pressure; MAP: Mean airway pressure; RR: Respiratory rate; TV: Tidal volume; FiO_2: Fraction of inspired oxygen; Ti: Inspiratory time; PS: Pressure support; PICU: Pediatric intensive care unit; LOS: Length of stay; PIM: Pediatric Index of Mortality; PRISM: Pediatric Risk of Mortality; PELOD: Pediatric Logistic Organ Dysfunction

used agents were dopamine (32.9%), adrenaline (24.3%), dobutamine (17.9%), noradrenaline (13.3%), and milrinone (6.9%). Neuromuscular blocking agents were required in 57 patients (32.9%).

Tracheostomy

Tracheostomy was present in 92 patients at some point during follow-up. Acute/temporary tracheostomy was performed in 4 patients (2.3%) and subsequently closed. In 88 patients, the indication for tracheostomy was chronic respiratory failure; 55 patients (31.8%) had tracheostomy at the time of admission. In 33 patients (19.1%), chronic respiratory failure was diagnosed during hospitalization, necessitating permanent tracheostomy. A total of 79 patients (45.7%) were discharged with home ventilators.

Complications and VAP

Complications were observed in 35 patients (20.2%). The most common complication was atelectasis (n=13, 7.5%), followed by VAP (n=12, 6.9%), pneumothorax (n=9, 5.2%), and decubitus ulcer (n=2, 1.2%) **(Table 3)**. The VAP rate was 4.46 per 1,000 ventilator days.

Table 3. Complications associated with mechanical ventilation

Complication	N	%
Atelectasis	13	7.5
Ventilator-associated pneumonia (VAP)	12	6.9
Pneumothorax	9	5.2
Decubitus ulcer	2	1.2
Total patients with ≥1 complication	35	20.2

Note: one patient had concurrent pneumothorax and VAP.

Mortality and factors associated with mortality

The overall PICU mortality rate was 2.43% (n=19 of all admissions). Among mechanically ventilated patients, the mortality rate was 11% (n=19/173). In univariate analysis, PIM II, PRISM III, and PELOD scores, the presence of neurological disease, need for invotropic support, and presence of tracheostomy were significantly associated with mortality **(Table 4)**. Longer MV duration was also associated with mortality (median 7 vs. 5 days, p=0.019), whereas age, sex,

PICU length of stay, neuromuscular blocker use, and weaning-onset day did not reach statistical significance. All 19 non-survivors had required inotropic/vasoactive support, and none of the 77 patients with neurological disease as the primary diagnosis died, suggesting a comparatively favorable mortality profile for this subgroup. These associations are univariate and hypothesis-generating; a multivariable model was not fitted given the limited number of events (n=19).

Table 4. Univariate comparison of survivors and non-survivors

Variable	Survivors (n=154)	Non-survivors (n=19)	p-value
PIM II, median (min-max)	23.4 (4.5-100)	100 (66.8-100)	<0.001
PRISM III, median (min-max)	17 (5-56)	45 (32-67)	<0.001
PELOD %, median (min-max)	1.3 (0.1-100)	76 (32-99)	<0.001
MV duration, days, median (min-max)	5 (1-61)	7 (2-61)	0.019
Age, months, median (min-max)	45 (1.8-216)	24 (2.4-180)	0.374
Sex, male, n (%)	87/154 (56.5%)	12/19 (63.2%)	0.758
Neurological disease, n (%)	77/154 (50.0%)	0/19 (0%)	<0.001
Inotropic/ vasoactive support, n (%)	36/154 (23.4%)	19/19 (100%)	<0.001
Tracheostomy, n (%)	91/154 (59.1%)	1/19 (5.3%)	<0.001
Neuromuscular blocker use, n (%)	48/154 (31.2%)	9/19 (47.4%)	0.247

DISCUSSION

The frequency of invasive MV use has steadily increased in PICUs worldwide. Contemporary studies report that over 20% of PICU patients require invasive ventilatory support (3), and up to 63% of patients admitted with acute respiratory or cardiorespiratory illness may ultimately require some form of MV (7). In the present study, the rate of MV application was 22.1%, which is consistent with figures reported in more recent single-center studies from Turkey, including Durak and Boydag who found an MV rate of 30.5% in a tertiary PICU (8), and with earlier domestic data from Robinder et al. (9) (30%), Kendirli et al. (10) (18.1%), and Poyrazoğlu et al. (11) (24.1%).

Regarding indications for MV, respiratory failure continues to be the most frequently reported indication across the literature (12,13). Farias et al. (12) reported respiratory failure in 75% of children, Ramirez et al. (13) in 46.5%, and Kendirli et al. (10) in 64%. In the present study, the frequency of MV due to respiratory failure was 62.4%, consistent with these reports. Neurological disease was the most prevalent underlying condition (44.5%), a finding also echoed in recent literature; Durak and Boydag similarly identified neurological diseases as the predominant diagnostic category among mechanically ventilated children (8).

Regarding ventilation modes, pressure-controlled ventilation remains the dominant strategy in pediatric practice. SIMV ± PS continues to be widely utilized, although the field has progressively moved toward volume-targeted modes to minimize VILI. The PEMVECC consensus recommends lung-protective strategies with tidal volumes of 5–8 mL/kg and plateau pressures below 28 cmH_2O (6). Şık reported SIMV ± PS use in 76.6% of cases in a Turkish PICU (14). In the present study, all patients were managed with pressure-controlled ventilation in SIMV+PS mode. The median tidal volume was 8 mL/kg (range 6-12), median PIP was 22 cmH_2O (range 11-44), and median PEEP was 6 cmH_2O — values broadly within the lung-protective range. Although volume-targeted modes have

been increasingly introduced in PICUs, their adoption remains limited in many centers.

MV complications remain a major source of morbidity in PICUs. Despite the use of lung-protective ventilation modes, complications occur frequently. Ramirez et al. (13) reported pneumothorax in 8.1% and VAP in 17.4% of patients; Kendirli et al. (10) found atelectasis in 26.3%, VAP in 17.5%, and pneumothorax in 13.1%; and Şık (14) reported an MV-related complication rate of 38.9%. In a recent retrospective study covering 2021–2023, 24.1% of patients experienced at least one adverse event, with VAP being the most common consequence (13%), followed by post-extubation stridor (7.9%) and air-leak syndrome (6%) (15). In the present study, complications were observed in 20.2% of patients; atelectasis was the most common complication (7.5%), followed by VAP (6.9%) and pneumothorax (5.2%). Ventilator parameters were largely maintained within lung-protective ranges across the cohort (median tidal volume 8 mL/kg, median PIP 22 cmH_2O, median PEEP 6 $cmH_{2v}O$). The comparatively low overall complication rate observed in this cohort is therefore likely attributable to a combination of generally protective ventilator settings and the VAP prevention bundle applied in this unit (see Methods), consistent with evidence that bundle-based prevention strategies significantly reduce VAP rates across settings (16); the VAP rate of 4.46 per 1,000 ventilator days observed here compares favorably with published benchmarks.

Sedation and analgesia protocols are fundamental to the management of mechanically ventilated children. In the present study, sedation was provided with midazolam in 126 patients (72.8%) and fentanyl in 87 patients (50.3%), representing the most frequently used agents — consistent with published pediatric sedation practices in which midazolam–opioid combinations remain the most common approach (6). Neuromuscular blocking agents were required in 57 patients (32.9%). Vasoactive support was required in 31.8% of patients, with dopamine and adrenaline being the most commonly used agents, consistent with standard practice for septic shock and low cardiac output states.

Mortality rates in PICUs vary considerably depending on institutional resources, patient case-mix, and underlying comorbidities. In PICUs, mortality rates have been reported to range from 4.7% to 19% (9,13). The mortality rate for patients receiving MV was reported as 47% by Tullu et al. (17), 58.3% by Kendirli et al. (10), and 36.4% by Şık (14). In a recent Turkish single-center study, a 19.4% mortality rate was observed among mechanically ventilated children with a statistically significant association with sepsis (8). In the present study, the overall PICU mortality rate was 2.43%, while mortality among mechanically ventilated patients was 11% — substantially lower than many comparative series. This favorable outcome likely reflects standardized care protocols, the relatively lower prevalence of sepsis-driven admissions, and the high proportion of neurological diagnoses, which may carry a different mortality profile.

In recent years, the prolonged need for MV has been reported as the most common indication for tracheostomy in children (18,19). In the present study, 21.4% (n=37) of patients underwent tracheostomy during hospitalization. Neurological diseases (76.1%) and metabolic diseases (12.5%) were the most common indications, consistent with reports by Jardine et

al. (20), Lawrason et al. (21), Mete et al. (19), and Karapınar et al. (22). A recent multicenter analysis further confirmed that tracheostomy rates are significantly associated with prolonged MV duration and that patients requiring MV for more than 30 days face considerably higher tracheostomy rates, VAP rates, and mortality (23). These findings reinforce the importance of early and systematic weaning assessment.

An important consideration when interpreting these findings is that the study period (February 2015–February 2016) preceded several major developments in pediatric respiratory support. Most notably, the Second Pediatric Acute Lung Injury Consensus Conference (PALICC-2), published in 2023, established the first internationally endorsed, evidence-graded definition and management bundle for pediatric acute respiratory distress syndrome (PARDS), with explicit targets for tidal volume, plateau pressure, driving pressure, and permissive hypercapnia (24). At the time of the present study, lung-protective ventilation was applied according to general physiological principles rather than a codified PARDS-specific protocol; the ventilator parameters recorded in this cohort nonetheless fell within the ranges now recommended by PALICC-2, suggesting that core lung-protective practices were already present in this unit before their formal consensus articulation.

The management of hypoxemic respiratory failure — the leading indication for MV in this cohort (51%) — has also evolved substantially over the past decade. High-flow nasal cannula (HFNC) therapy has become markedly more widely adopted as a first-line intervention to avert or delay invasive ventilation (25), but was not systematically used in the study PICU during data collection. Its subsequent adoption may have shifted the invasively ventilated population toward higher-severity cases in contemporary practice, a consideration when extrapolating these findings to current populations.

These historical figures find support in a recently published Swedish PICU cohort study covering a similarly dated period (2008–2016), which reported mortality within a comparable range despite being published in 2024 (26), and recent reviews confirm that prolonged MV remains the leading driver of pediatric tracheostomy, reinforcing the continued relevance of these findings to current practice (27).

Limitations of the study

An important limitation of this study is that the data were collected approximately 10 years ago (February 2015–February 2016). Over the past decade, MV practices have evolved substantially, particularly with the increased use of non-invasive modalities, standardization of lung-protective strategies, and advances in ventilator technology. Therefore, the findings may not fully reflect current clinical practice. Nevertheless, the study provides valuable historical insight and may serve as a benchmark for evaluating temporal changes in pediatric MV in Turkey. The single-center design and the one-year observation window additionally limit the generalizability of findings. In addition, cuff leak testing prior to extubation was not systematically recorded during the study period; therefore, its relationship with post-extubation stridor could not be evaluated, and this remains an area for prospective assessment in future studies.

CONCLUSION

The pediatric severity scores PIM II, PRISM III, and PELOD were each strongly and independently associated with in-hospital mortality, supporting their continued use as prognostic tools in PICU practice. Ventilator management and outcomes

were broadly comparable to contemporary series, despite the data predating several subsequent advances in pediatric respiratory support. Multicenter prospective studies incorporating contemporary practices are needed to validate these findings and generate robust national data on pediatric MV outcomes in Turkey.

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Conflict of Interest

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Previous Presentation

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Author Contributions

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