Research Article / Araştırma Makalesi

Survival Following Percutaneous Endoscopic Gastrostomy in Neurology Intensive Care Unit Patients

Nöroloji Yoğun Bakım Ünitesindeki Hastalarda Perkütan Endoskopik Gastrostomi Sonrası Sağkalım

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Abstract

Background: We aimed to determine factors affecting mortality and survival after Percutaneous endoscopic gastrostomy (PEG) in patients who were hospitalized in the neurology intensive care unit during the coronavirus disease-2019 (COVID-19) pandemic.
Materials and Methods: The clinical and demographic data of 29 patients aged 18 years and older who received PEG tube insertion during hospitalization in the Neurology Intensive Care Unit of Bursa City Hospital, Turkey, between February 2020 and May 2021 were examined retrospectively. Patients' demographics, clinical characteristics, and survival status were recorded.
Results: We included 29 patients (16 females and 13 males) into our study. Median age was 71 (33–89) years among survivors and 75.5 (48–90) years among those who died. The groups were similar with respect to age (p = 0.119) and sex (p = 0.806). Mortality rate after PEG insertion was 66%. Mean overall survival after PEG tube insertion was 129.49 days (95% CI: 91.21–167.78). Cox regression revealed that having multiple comorbidities was associated with increased the likelihood of mortality by 2.822-fold (95% CI: 1.001–7.968, p = 0.049).
Conclusions: These findings show that having multiple comorbidities was the most important factor associated with mortality among PEG recipients who were admitted to the Neurology Intensive Care Unit during the COVID-19 pandemic. Since multiple comorbidities cause shorter survival, it appears that the decision to insert PEG tubes must be made extremely cautiously among these patients. However, more comprehensive studies should be conducted to clarify the effect of COVID-19 on mortality rates and survival time after PEG.

Key Words: Percutaneous endoscopic gastrostomy, COVID-19 pandemic, Comorbidity, Mortality, Survival

Öz

Amaç: Koronavirüs hastalığı-2019 (COVID-19) pandemisi sırasında nöroloji yoğun bakım ünitesinde yatan hastalarda Perkütan endoskopik gastrostomi (PEG) sonrası mortalite ve sağkalımı etkileyen faktörleri belirlemeyi amaçladık.
Materyal ve Metod: Türkiye'de Bursa Şehir Hastanesi Nöroloji Yoğun Bakım Ünitesinde Şubat 2020 ile Mayıs 2021 tarihleri arasında yatışı sırasında PEG tüpü takılan 18 yaş ve üzeri 29 hastanın klinik ve demografik verileri geriye dönük olarak incelendi. Hastaların demografik özellikleri, klinik özellikleri ve sağkalım durumları kaydedildi.
Bulgular: Çalışmamıza 29 hasta (16 kadın ve 13 erkek) dahil edildi. Ortanca yaş hayatta kalanlar arasında 71 (33-89) ve ölenler arasında 75,5 (48-90) idi. Gruplar yaş (p = 0.119) ve cinsiyet (p = 0.806) açısından benzerdi. PEG yerleştirilmesinden sonra ölüm oranı %66 idi. PEG tüpünün yerleştirilmesinden sonra ortalama genel sağkalım 129.49 gündü (%95 GA: 91.21–167.78). Cox regresyonu, birden fazla komorbiditeye sahip olmanın mortalite olasılığını 2.822 kat arttırdığını ortaya koydu (%95 GA: 1.001-7.968, p = 0.049).
Sonuç: Bu bulgular, COVID-19 pandemisi sırasında Nöroloji Yoğun Bakım Ünitesi'ne kabul edilen ve PEG tüpü takılan olgularda mortalite ile ilişkili en önemli faktörün birden fazla komorbiditeye sahip olması olduğunu göstermektedir. Çoklu komorbiditeler daha kısa sağ kalıma neden olduğundan, bu hastalarda PEG tüpü yerleştirme kararının son derece dikkatli verilmesi gerektiği görülmektedir. Ancak COVID-19'un PEG sonrası ölüm oranları ve sağkalım süresi üzerindeki etkisini netleştirmek için daha kapsamlı çalışmalar yapılmalıdır.

Anahtar Kelimeler: Perkütan endoskopik gastrostomi, COVID-19 pandemisi, Komorbidite, Mortalite, Sağkalım

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Introduction

Enteral nutrition (EN) and parenteral nutrition (PN) are used for nutritional support to meet the metabolic needs of patients with inadequate oral intake in the intensive care unit (ICU). PN has various disadvantages, including intravenous route risks, high cost, and compromise of the intestinal barrier due to the inability to provide enteral stimulation. For these reasons, EN is generally preferred over PN in patients with a functional gastrointestinal system (1,2). Nasoenteric nutrition is used as the first choice for EN in patients where oral intake is not possible; however, due to various adverse effects such as irritation, ulceration, bleeding, esophageal reflux and aspiration pneumonia with the use of nasoenteric nutrition, percutaneous endoscopic gastrostomy (PEG) is preferred, especially in patients who require EN for more than 2–4 weeks (2-5).

Briefly, PEG is defined as "the endoscopic placement of a flexible tube to create a temporary or permanent connection between the abdominal wall and the gastric cavity to allow direct passage of food into the patient's digestive tract" (6). As mentioned previously, PEG is an important nutritional alternative for patients hospitalized in the ICU, especially among those hospitalized for neurological causes. Motor neuron diseases such as amyotrophic lateral sclerosis, cerebral palsy, bulbar palsy, cerebrovascular disease, dementia, and reduced level of consciousness due to severe cerebral injury are the most common neurological indications of PEG (2). In studies exploring the frequency of mortality after PEG, it has been reported that PEG does not increase mortality and significantly reduces the length of stay in hospital, while the presence of comorbidity and/or conditions necessitating PEG insertion are associated with increased mortality and shorter survival (7-11). Considering its effects on ICU employees (12,13), ICU patient turnover (14,15) and patient care (16,17), it is necessary to assess how the coronavirus disease-2019 (COVID-19) pandemic has influenced mortality in relation with ICU-related factors among patients. One particular concern for the field of neurology is whether the COVID-19 pandemic influenced mortality rates following PEG insertion as this is an invasive intervention that could increase the likelihood of infection. Therefore, it is important to re-evaluate mortality rates after PEG and risk factors during the pandemic, and to devise new measures to reduce risks associated with PEG insertion if necessary.

In this study, we aimed to identify risk factors independently associated with mortality and survival time after PEG insertion in patients who were hospitalized in the neurology ICU during the COVID-19 pandemic.

Materials and Methods

In this study, the clinical and demographic data of 29 patients aged 18 years and older in whom PEG tube insertion was performed during hospitalization in the Neurology ICU of Bursa City Hospital, Turkey, between February 2020 and May 2021, were examined retrospectively. The study was initiated with the approval of Clinical Research Ethics Committee of Bursa City Hospital, and was carried out in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from patients or legal proxy decision makers.

Data collection

Age, sex, primary disease, comorbidities, number of PEG tubes used, causes of delays in PEG insertion, time until PEG insertion after hospitalization (days), length of stay in hospital before and after PEG, cause of death and its place (in-hospital, after discharge), complications that may be associated with PEG, and information regarding invasive mechanical ventilation and overall survival were obtained from hospital records. Covid-19 pneumonia was considered as a separate comorbidity.

Patient selection

As the criteria for PEG tube insertion, it was determined that oral intake would not be taken for at least 4 weeks or later, or that oral intake was not taken for 4 weeks or more and consent was obtained from the patients or their legal proxy decision makers (5). PEG tube was inserted in 29 patients who met these criteria. Insertion of the PEG tube after 4 weeks was determined as a delay. Mortality related to the PEG procedure (during and after the procedure) and mortality due to the complications of the procedure were defined as PEG-related mortality.

PEG tube insertion

Informed consent for PEG insertion was obtained by healthcare professionals based on consent from patients or legal proxy decision makers. In patients receiving warfarin due to thromboembolic complication risks, treatment was discontinued 5 days before the PEG procedure and bridging treatment was carried out with low molecular weight heparin (LMWH) or unfractionated heparin (UFH). LMWH was discontinued 8 hours prior to the PEG procedure; UFH infusion was stopped 6 hours before PEG and was restarted 6 hours after the procedure was completed (18). For peristomal infection and septic complications prophylaxis, 1 gr of cefazolin was administered intravenously 30 minutes before the procedure. The patients were placed on their backs. PEG tube was used in all patients.

After appropriate sedation, analgesia and local anesthetic application, the abdominal skin was disinfected with an appropriate disinfectant, oral secretions were aspirated, and the oropharyngeal cavity was disinfected with an appropriate antiseptic solution. The Pull-through method was utilized for all procedures (11). Esophagogastroduodenoscopy was performed to widen the gastric wall with maximum air/carbon dioxide insufflation. The needle insertion site (targeted as the lower part of the stomach) was determined via gastroscopic transillumination together with palpation. A needle was inserted through the skin into the stomach from this site. Then, a guidewire was introduced into the stomach and fixed with an endoscopic clamp or forceps. The endoscope was then slowly withdrawn until the guidewire was visible in the patient's mouth and it was fixed to the PEG tube. The PEG tube

was inserted with the aid of the guidewire, ensuring that it reached its target position through the stomach. Control endoscopic imaging was performed. Feeding from PEG was initiated six hours after successful procedures (6,19).

Statistical analysis

All analyses were performed on the SPSS software (version 21, IBM, Armonk, NY). We used Q-Q and histogram plots to assess the distribution characteristics of continuous variables. Data are given as median (minimum - maximum) for continuous variables as deemed necessary by non-normal distributions in continuous variables, while frequency and percentage values were depicted for categorical variables. Since continuous variable distributions were non-normal, the Mann-Whitney *U* test was employed for comparisons between groups. Categorical variables were analyzed with appropriate chi-square tests or the Fisher's exact test. Survival times were calculated with the Kaplan Meier method. Intergroup comparison of survival times were performed with the Log rank test. Cox regression analysis (forward conditional method) were performed to determine significant prognostic factors associated with mortality. Two-tailed p-values of less than 0.05 were considered statistically significant.

Results

We included 29 patients (16 females and 13 males) into our study. Median age was 73 (range 33–90) years in the study group; survivors had a median age of 71 (33–89), while those who died had a median age of 75.5 (48–90) years. There were no significant differences between the surviving and mortality groups in terms of age (p = 0.119) and sex (p = 0.806). The groups were also similar with regard to primary disease (cerebrovascular disease: p = 0.192, Alzheimer / dementia: p = 0.573, amyotrophic lateral sclerosis: p = 0.448), comorbidities (diabetes mellitus: p = 0.697, hypertension: p = 0.396, heart disease: p = 1.000, pneumonia / COVID-19: p = 0.185), number of comorbidities (p = 0.185), complications (p = 1.000), number of PEG tubes (p = 1.000), delay in PEG insertion (p = 1.000), length of stay in hospital before PEG tube (p = 0.051), length of stay in hospital after PEG tube (p = 1.000), and total length of stay in hospital (p = 0.357) (Table 1).

The mortality rate after PEG was 66%. Mean overall survival time after PEG tube insertion was 129.49 (95% CI: 91.21 - 167.78) days. Survival was significantly shorter in patients with multiple comorbidities than in patients with a single comorbidity (p = 0.041). There were no significant differences between the groups in terms of survival times with regard to age (p = 0.145), sex (p = 0.631), diabetes mellitus (p = 0.202), hypertension (p = 0.318), heart disease (p = 0.653), pneumonia / COVID-19 (p = 0.079) and delay in PEG tube insertion (p = 0.682) (Table 2, Figure 1, Figure 2).

We performed cox regression analysis to determine significant prognostic factors of the mortality and found that having multiple comorbidities (≥2) was a poor prognostic factor. Patients with multiple comorbidity had 2.822-fold greater risk of death than those without (HR: 2.822, 95% CI: 1.001 - 7.968, p = 0.049). Other variables included in the model, age (p = 0.326), sex (p = 0.602), diabetes mellitus (p = 0.988), hypertension (p = 0.741), heart disease (p = 0.460), pneumonia / COVID-19 (p = 0.338), delay in PEG tube insertion (p = 0.499) and time until PEG tube insertion after hospitalization (p = 0.052) were found to be non-significant (Table 3).

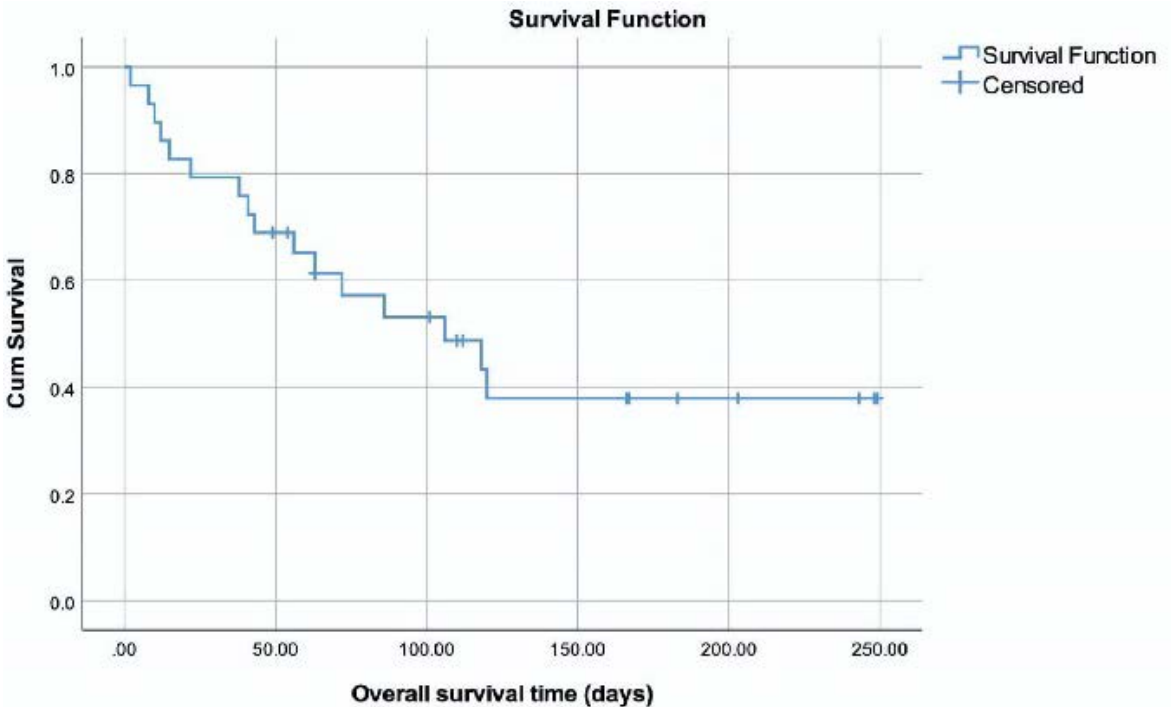

Figure 1. Overall survival plot

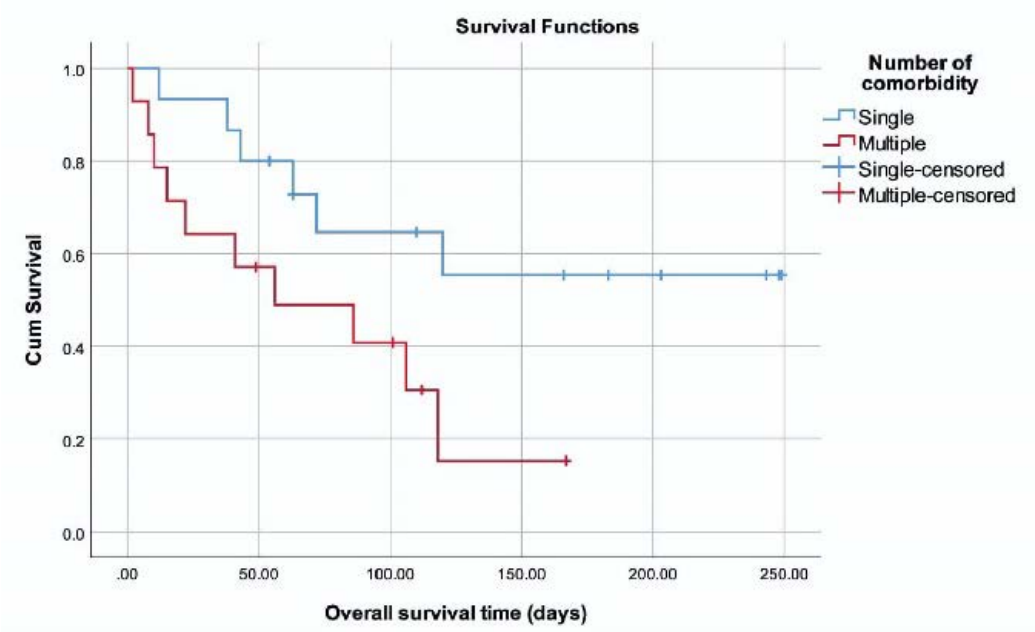

Figure 2. Overall survival plot with regard to number of comorbidities

Table 1. Summary of patient characteristics with regard to mortality

	Status			
	Alive (n=13)	**Exitus (n=16)**	**Total (n=29)**	**p**
Age	71 (33 - 89)	75.5 (48 - 90)	73 (33 - 90)	0.119
Sex				
Female	8 (61.54%)	8 (50.00%)	16 (55.17%)	0.806
Male	5 (38.46%)	8 (50.00%)	13 (44.83%)	
Diagnosis [(1)]				
Cerebrovascular disease	11 (84.62%)	16 (100.00%)	27 (93.10%)	0.192
Alzheimer / Dementia	2 (15.38%)	1 (6.25%)	3 (10.34%)	0.573
Amyotrophic lateral sclerosis	1 (7.69%)	0 (0.00%)	1 (3.45%)	0.448
Comorbidities [(1)]				
Diabetes mellitus	3 (23.08%)	5 (31.25%)	8 (27.59%)	0.697
Hypertension	6 (46.15%)	11 (68.75%)	17 (58.62%)	0.396
Heart diseases	5 (38.46%)	7 (43.75%)	12 (41.38%)	1.000
Pneumonia / COVID-19	4 (30.77%)	10 (62.50%)	14 (48.28%)	0.185
Number of comorbidities				
Single	9 (69.23%)	6 (37.50%)	15 (51.72%)	0.185
Multiple	4 (30.77%)	10 (62.50%)	14 (48.28%)	
Complication				
Bleeding / Leakage	1 (7.69%)	2 (12.50%)	3 (10.34%)	1.000
Other	0 (0.00%)	0 (0.00%)	0 (0.00%)	
Number of PEG tubes				
1	13 (100.00%)	15 (93.75%)	28 (96.55%)	1.000
2	0 (0.00%)	1 (6.25%)	1 (3.45%)	
Delay in PEG insertion [(1)]	7 (53.85%)	8 (50.00%)	15 (51.72%)	1.000
Family approval	4 (30.77%)	3 (18.75%)	7 (24.14%)	0.667
Pneumonia / COVID-19	3 (23.08%)	7 (43.75%)	10 (34.48%)	0.433
Sepsis / Infection	1 (7.69%)	1 (6.25%)	2 (6.90%)	1.000
Length of stay in hospital, before PEG tube	23 (10 - 88)	18.5 (7 - 56)	20 (7 - 88)	0.051
Length of stay in hospital, after PEG tube	28 (14 - 57)	30 (2 - 118)	28 (2 - 118)	1.000
Length of stay in hospital	74 (25 - 123)	49.5 (15 - 174)	59 (15 - 174)	0.357
Time between PEG tube and death	-	42 (2 - 120)	42 (2 - 120)	N/A
Time between hospitalization and death	-	60.5 (16 - 174)	60.5 (16 - 174)	N/A
Cause of death [(1)]				
Myocardial infarction	-	7 (43.75%)	7 (43.75%)	N/A
Pneumonia / COVID-19	-	11 (68.75%)	11 (68.75%)	N/A
Sepsis / Infection	-	7 (43.75%)	7 (43.75%)	N/A
Location of death				
In hospital	-	14 (87.50%)	14 (87.50%)	N/A
After discharge	-	2 (12.50%)	2 (12.50%)	

Data are given as mean ± standard deviation or median (minimum - maximum) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables. (1) Patients may have more than one of the below.

Table 2. Survival times after PEG tube insertion (days) with Kaplan Meier method and comparisons of groups with the Log rank test

	n	Exitus	Mean (95% CI)	p
Overall survival	29	16	129.49 (91.21 - 167.78)	N/A
Age				
< 70	9	3	175.08 (109.46 - 240.70)	0.145
≥ 70	20	13	108.19 (65.20 - 151.17)	
Sex				
Female	16	8	137.54 (84.63 - 190.46)	0.631
Male	13	8	118.58 (63.98 - 173.18)	
Diabetes mellitus				
Absent	21	11	141.79 (99.20 - 184.39)	0.202
Present	8	5	74.38 (23.98 - 124.77)	
Hypertension				
Absent	12	5	155.61 (94.38 - 216.84)	0.318
Present	17	11	109.28 (63.70 - 154.85)	
Heart diseases				
Absent	17	9	133.43 (85.87 - 181.00)	0.653
Present	12	7	122.26 (61.58 - 182.94)	
Pneumonia / COVID-19				
Absent	15	6	162.24 (108.53 - 215.95)	0.079
Present	14	10	79.70 (47.80 - 111.61)	
Number of comorbidities				
Single	15	6	165.66 (114.53 - 216.78)	0.041
Multiple	14	10	73.03 (41.69 - 104.37)	
Delay of PEG tube				
Absent	14	8	121.54 (63.75 - 179.33)	0.682
Present	15	8	134.55 (84.41 - 184.69)	

CI: Confidence interval

Table 3. *Significant factors associated with mortality, Cox regression analysis*

	β Coefficient	*Std Error*	*p*	*Exp(β)*	*95.0% CI for Exp(β)*	
					Lower	*Upper*
Multiple comorbidity	*1.038*	*0.530*	*0.049*	*2.822*	*1.001*	*7.968*

CI: Confidence interval

Other parameters added to the model, age (p = 0.326), sex (p = 0.602), diabetes mellitus (p = 0.988), hypertension (p = 0.741), heart disease (p = 0.460), pneumonia / COVID-19 (p = 0.338), delay in PEG tube insertion (p = 0.499) and time until PEG tube insertion after hospitalization (p = 0.052), were found to be non-significant

Discussion

Although enteral nutrition can be delayed up to the tenth day (beginning of severe protein catabolism) in patients requiring enteral feeding, early administration of enteral nutrition is necessary to ensure adequate nutrition in patients with insufficient oral intake. Thus, PEG should be considered in patients with inadequate oral intake given that they have a functional gastrointestinal tract and if it is safe to sustain gastrointestinal tube placement (2). The number of patients who can medically benefit from PEG placement is quite high, however, post-PEG deaths and their causes and appropriate patient selection for PEG are subjects of interest (19-21). Risk for increased likelihood of COVID-19 infection or other problems (including sustainability of PEG) in such patients is a factor that should be assessed with regard to its influence on post-PEG mortality. According to the results we obtained in this study, COVID-19 was not significantly associated with mortality or length of survival among PEG recipients admitted to the Neurology ICU. Cox regression revealed that the only factor independently associated with increased mortality risk after PEG insertion during the COVID-19 pandemic was having multiple comorbidities. Also, patients with multiple comorbidities were found to have shorter survival compared to those with a single comorbidity.

PEG is considered a minimally invasive procedure requiring easily accessible instrumentation and does not necessitate general anesthesia (6). Studies examining mortality rates and causes, factors affecting survival time and the effects of PEG on survival have often yielded similar results. In one study, 30-day survival percentage after PEG was 11.4%, 365-day survival percentage was 47.1%, and mean survival time was 110 days. It was emphasized that none of the deaths had occurred due to PEG placement (8). Schneider et al. reported a 10% 30-day mortality rate after PEG regardless of the PEG procedure and its complications, and they emphasized that opening PEG for neurological reasons increased this rate (22). Survival analysis of 268 PEG recipients in a retrospective cohort showed an early mortality rate of 5.2% and a median survival of 801 days after PEG (23). Arora et al. showed that each year of increase in age increased risk of death by 1% among PEG recipients (24). In another study,

being older than 75 years was defined as a predictive factor for early death (1 month after PEG insertion). In the same study, the presence of at least three additional risk factors (among congestive heart failure, kidney failure, urinary tract infection, previous aspiration, chronic lung disease, coagulopathy, pulmonary circulation disorders, metastatic cancer and liver disease) was found to cause a 6-fold increase in the likelihood of death within 1 month when compared to patients without any of these risk factors (10). Interestingly, our study showed that having more than one comorbidity significantly shortened survival and increased mortality risk compared to those with a single comorbidity, which appears to be in support of the aforementioned study –despite limited patient count.

With respect to the effects of specific diseases, patients with head and neck cancer were shown to have a higher risk of procedure-related death following PEG compared to other patient populations (25). The influence of PEG on the survival of dementia patients has also been examined; however, results did not show a difference between patients with and without PEG insertion (26). The benefits of PEG feeding in patients over 80 years of age with comorbidities such as diabetes and advanced dementia remain unclear (27,28). In a prospective study of 484 patients who had PEG implantation for various reasons, it was reported that 18% of all patients died within 2 months after PEG placement, while short-term mortality rate was 22% in the neurological disease group. In addition, although complications after PEG increase the short-term mortality rate, it was emphasized that the most important factor in mortality is underlying disease(s) that create the need for PEG, especially cancer and neurological diseases (11). In another study, it was demonstrated that the combination of low albumin and high C-reactive protein levels predicted a high risk of early death after PEG (29). Multivariate regression analysis results of a comprehensive study of 1234 PEG implanted patients showed that low BMI, low serum albumin levels, and active cancer were independent risk factors for deaths occurring within 60 days (30). In another retrospective study, protein malnutrition, documented infection prior to the procedure, or cardiovascular disease were not found to be associated with mortality or complications (9). In a population-based study conducted in the USA, it was reported that 10.8% of 181.196 patients who underwent PEG died during hospitalization. According to the multivariate analysis results of this study, presence of CHF, chronic lung disease, kidney failure, coagulopathy, pulmonary circulation disorders, metastatic cancer, liver disease, and fluid and electrolyte disorders increase the risk of death after PEG, and conversely, diabetes, obesity, deficiency anemia, hypertension, stroke, other neurological disorders, psychoses and the presence of depression were shown to be independently associated with decreased mortality (24). In our study, the overall mortality rate after PEG was 66%, and the mean overall survival of these patients was 129 days. The reason for higher mortality rate compared to other studies may be caused by the low number of patients. The current study showed that the only significant prognostic factor associated with mortality was having multiple comorbidities. When assessing the risk of death after PEG, we cannot ignore that the mortality risk of many patients who require PEG is higher than that of individuals with comorbidities but do not require PEG. Although it has not been universally proven that PEG feeding reduces the risk of aspiration pneumonia or long-term mortality and produces better outcomes in weight control compared to nasogastric tube feeding, the endoscopic procedure is thought to be more effective and safer than nasogastric tube feeding (6).

A significant portion of COVID-19 patients were followed in ICUs due to respiratory failure. Gastric tubes were initially used for enteral feeding in these patients, but PEG insertion is recommended in patients with continued need after 2-4 weeks (1-3,5). However, as a natural consequence of the pandemic, PEG insertion may be delayed for various reasons such as the use of therapeutic anticoagulation and the delay in obtaining consent, both in COVID-19 patients and in other indications requiring PEG insertion (31-33). The effect of this delay on mortality after PEG was not found to be significant in the present study. In a retrospective cohort, it was shown that there was no significant difference between early PEG tube insertion (within 14 days) and late insertion (after 14 days) in terms of 30-day mortality and complications, but early PEG was associated with a shorter length of stay (7). Reddy and colleagues compared the outcomes of early (7 days post stroke) and late PEG (>7 days post stroke) in stroke patients. They showed that, hospital length of stay was significantly shorter in patients with early PEG tube placement (9). In our study, although there was no statistically significant relationship between PEG delay and mortality and survival time, it should be emphasized that pneumonia due to COVID-19 may be a primary cause of PEG delay. Demonstrating the harms of PEG delay with more detailed studies including a greater number of patients can elucidate the importance of this COVID-19-related problem.

Our study has some limitations. First, being a retrospective study, patient assessments were reliant upon accurate record-keeping which may have been problematic during the COVID-19 pandemic because of extreme workloads. Second, the small number of participants and the fact that it was a single-centered study limits the generalizability of the results. Finally, lack of a control group and a scoring system to assess the general health status of patients are omissions that could have affected the comparison of groups. In order to confirm the results of this study, more comprehensive studies with a multicenter, prospective design that include stratified patient groups are needed.

Conclusion

Our study, which was conducted during the COVID-19 pandemic in a Neurology ICU, showed that having multiple comorbidities was associated with shorter survival and was an independent risk factor for mortality. Due to the low

long-term survival rates of patients with various comorbidities, this should be taken into account when making the decision for PEG use, especially during the COVID-19 pandemic. However, more comprehensive studies should be conducted to clarify the effect of COVID-19 on mortality rates and survival time after PEG.

Ethical Approval: *The study was initiated with the approval of Clinical Research Ethics Committee of Bursa City Hospital (decision number: 2021-10/4, date: 02.06 2021), and was carried out in accordance with the principles of the Declaration of Helsinki.*

Author Contributions:
Concept: M.A.B., C.H.
Literature Review: M.A.B., C.H.
Design : M.A.B., C.H.
Data acquisition: M.A.B., C.H.
Analysis and interpretation: M.A.B., C.H.
Writing manuscript: M.A.B., C.H.
Critical revision of manuscript: M.A.B., C.H.
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