Is Percutaneous Endoscopic Gastrostomy Tube Feeding Beneficial for Improving Survival in Patients With Dementia? A Systematic Review and Meta-Analysis of Current Pieces of Evidence

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Abstract- Dementia is a progressive, disabling neurogenic disease that results in serious nutritional deficiencies included dysphagia, malnutrition, and weight loss. The Percutaneous Endoscopic Gastrostomy (PEG) is a long-term enteral feeding method that is routinely used in demented patients with poor food intake as a standard protocol. However, most of the pieces of evidence have not shown the beneficial effects of PEG feeding on complications or survival rates in these patients. Some studies have even reported an increase in mortality. The current systematic review and meta-analysis aimed to evaluate the mortality rate and survival in primary demented patients with PEG. A systematic search was conducted on Pubmed and Scopus databases up to Aug 2019. The data were reviewed according to the Cochrane handbook and preferred reporting items for systematic reviews and meta-analyses (PRISMA) and meta-analysis of observational studies in epidemiology (MOOSE). Based on the random-effects model, the mortality rate and median survival were expressed as risk ratio and weighted mean difference (WMD) and 95% CI, respectively. Among 13 included studies, PEG insertion in patients with primary dementia has no significant effect on 30-day, 90-day, 180-day, 1-year, and 2- year mortality rate or median survival (WMD: 9.77; 95% CI: -22.43 to 41.98; *P*=0.55). It seems that nasogastric tube (NGT) feeding in compared to PEG in this population is more effective. In conclusion, further prospective studies are needed for comprehensive evaluation of mortality or survival regarding comorbidities, underlying disease, cognitive and physical performance, and nutritional problems in demented patients.

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Keywords: Dementia; Mortality; Survival; Nutrition support; Percutaneous endoscopic gastrostomy (PEG)

Introduction

Dementia is a progressive, disabling neurogenic disease derived from neuron damage in the brain (1). Patients with dementia often need hospitalization care which exerts a lot of costs on the medical system (2). Dementia often leads to serious nutritional deficiencies because the patients with dementia are progressively losing their ability to chew, swallow, or in advanced stages, even they cannot recognize food or eating components (3,4), resulting in dehydration, malnutrition, and weight loss (5).

In dementia patients with the nutritional problem, percutaneous endoscopic gastrostomy (PEG) usually is inserted, although its beneficial effects are unclear (6). On the basis of pieces of evidence, the PEG, which is a long-term enteral feeding method of administration, can improve nutritional status in patients with inadequate

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intake in neurogenic disorders (7). In a population with dementia, while the PEG feeding tube placement is accepted as a standard care method in many health professionals, the pieces of evidence which evaluating the outcome of PEG feeding in dementia patients with poor food intake, malnutrition and who with nutritional difficulties reported no positive effects on survival rate (8). On the other hand, the most existing observation had revealed no harmful outcomes from PEG method usage in patients with dementia compared with non-dementia patients (9).

In view of the contradictory effects of PEG insertion on survival as a routine method in dementia patients and regarding limited data from previous pieces of evidence, the present study for the first time amid to perform a systematic review and meta-analysis of all relevant published studies to clarify the effects of PEG tube feeding on mortality rate and median survival in primary dementia patients.

Materials and Methods

Literature screening and systematic search strategy

The Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) (10) and Meta-analysis of Observational Studies in Epidemiology (MOOSE) (11) instruction was used in the present systematic review and meta-analysis. A systematically computerized search was performed on PubMed and SCOPUS up to Aug 2019 publications in the English language. The Medical subject headings (MeSH) and non-MeSH keywords used for search process were included Mental Disorders [Title/Abstract] OR Cognitive Dysfunction [Title/Abstract] OR Alzheimer Disease [Title/Abstract] OR Dementia [Title/Abstract] AND enteral feeding [Title/Abstract] OR gastrostomy [Title/Abstract] OR Percutaneous endoscopic gastrostomy [Title/Abstract] OR PEG [Title/Abstract]. The references section of all eligible articles, as well as reviews or systematic reviews, was checked manually to avoid missing any related data. In the next step, after importing relevant publications to the EndNote document management software (Clarivate Analytics), the duplicate data were detected and removed. We excluded laboratory studies (in vitro, in vivo, or ex-vivo studies), animal studies, conference papers, and review articles based on eligibility and exclusion criteria. The eligible studies were enrolled in this meta-analysis after reviewing their abstract or full-text.

Eligibility and exclusion criteria

At the present meta-analysis, we included the articles which met the following eligibility criteria: I) The studies with full-text in English language II) Intervention with PEG as enteral tube feeding and III) The publications which reported sufficient information in the case of mortality rate and median survival at the intervention in PEG and control groups.

The studies with any following defined exclusion criteria were excluded from our meta-analysis: I) laboratory research (in vitro, in vivo, or ex-vivo) or animals studies, II) studies which not performed on elderly patients III) studies with no enough data about mortality rate and survival in demented patients with PEG or control group IV) Studies on the effect of any other supplemental feeding method along with PEG in the intervention group but not in the control group and VI) Studies which had no control group.

Data selection and extraction

At the current systematic review and meta-analysis, the data from defined included studies were extracted indecently by two reviewers (M.S. and M.A.). Any possible disagreement was solved after discussing or based on a third reviewer (R.H.) consensus. To continue, the following data extracted from all included studies: the first author name, the publication year, the country of study, the sample size, the design of studies, the gender of participants, mean age, the population type, the intervention feeding type, complications, risk ratio of 30-day, 90-day, 180-day, 1-year, and 2-year mortality as well as mean±standard deviation (SD) of median survival.

Quality assessment

The quality of observational studies was assessed according to the Newcastle-Ottawa Quality Assessment Scale included the following factors: I) Patient selection, II) comparability of the study groups, and III) assessment of outcome. Each study had a score of 0-9, and the studies that achieved six scores or more stars were considered high quality (12) (Table 1).

Statistical analysis

At the current work, Review Manager 5.3.5 (The Nordic Cochrane Center, The Cochrane Collaboration) software was applied to statistical data analysis. The mortality rate (30-days, 90-days, 180-days, one-year, and two-year mortality), as well as median survival days, were considered as continuous variables, and in continue, according to random-effects model, mortality rate and median survival were expressed as risk ratio

and weighted mean difference (WMD) and 95% confidence interval (CI) respectively. The heterogeneity or homogeneity among included studies was identified based on Cochrane's Q test and I^2 statistical test; If $P<0.1$ and $I^2>50\%$, the study defined heterogeneous, and If $P>0.1$ and $I^2\leq 50\%$, the data accounted homogenously. In addition, the potential heterogeneity sources were detected by subgroup analyses (13) consisting of disease, feeding method, and age. It is necessary to mention, in the studies that the mortality rate was not available, we calculated mortality rates in groups using Kaplan-Meier graph and *WebPlotDigitizer online software as well as the studies which* median survival and range were not clarified (13,14). Then, the median and range were converted to mean and standard deviation according to the method devised by Hozo *et al*., (15). The $P<0.05$ accounted as statistically significant in the analysis.

Table 1. Quality assessment of studies[a]

Study source	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at the start of the study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur (>=5 years)	Adequacy of follow up of cohorts (>80 %)	Total score
Nair et al. 2000	1	0	1	1	1	0	0	1	5
Sanders et al. 2000	1	1	1	1	1	0	1	1	7
Dwolatzky et al. 2001	1	1	1	1	1	0	1	1	7
Meier et al. 2001	1	1	1	1	2	1	0	1	8
Paillaud et al. 2002	1	1	0	1	1	0	0	1	5
Murphy et al. 2003	1	1	1	1	1	0	1	1	7
Rimon et al. 2005	1	1	0	1	1	0	1	1	6
Malmgren et al. 2011	1	1	0	1	1	0	1	1	6
Kumagai et al. 2012	1	1	0	1	2	0	1	0	6
Atencio et al. 2015	1	1	1	1	1	0	1	1	7
Ticinesi et al. 2016	0	1	0	1	2	0	1	1	6
Takayama et al. 2017	1	1	1	1	2	0	1	0	7
Tomioka et al. 2017	1	1	1	1	1	0	1	1	7

[a]The study quality was assessed according to the Newcastle Ottawa Quality assessment scale for cohort studies. This scale awards a maximum of 9 points to each study: 4 for selection, 2 for comparability, and 3 for assessment of outcomes (for cohort study). 1 = "Yes", 0 = "No", "Unable to determine," or "Not available

Results

Literature search

The flow diagram of publications in (Figure 1) is illustrated according to the Quality of Reporting of Meta-analyses statements. Overall, 13 studies were included at present systematic review and meta-analysis. Two articles reported mortality in dementia patients who had PEG feeding tubes (16,17), ten studies reported survival rate (18-27), and one reported both mortality rate and survival in this population (28).

At the searching of the primary database, 11377 related data were identified (762 in PubMed and 10610 in Scopus). In continue, manual searches of related articles were enrolled five additional studies in the present systematic review and meta-analysis. In the next step, the duplicated studies were determined and removed using Endnote software (n=742).

The title and abstract of the remaining publications (10635) were reviewed to determine included studies. The following studies were excluded from this work (totally 10574):

Unrelated studies (n=7891), disorders other than dementia (872), the Data from patients with dementia were combined with other diseases (n=166), animal or in vitro studies (n=1053), case reports (261), and review articles (n=249). Sixty-one articles selected, and their eligibility was evaluated exactly through a review of their full text.

Finally, 13 articles included to meta-analysis after studies with the following characteristics were excluded (totally n=48): Full text not found (n=5), non-English full-texts (n=12), without expected outcomes (n=15), PEG was administered in combination with a nasogastric tube (NGT) or other alternative nutrition (n=8) and the data from patients with dementia were combined with other diseases (n=8).

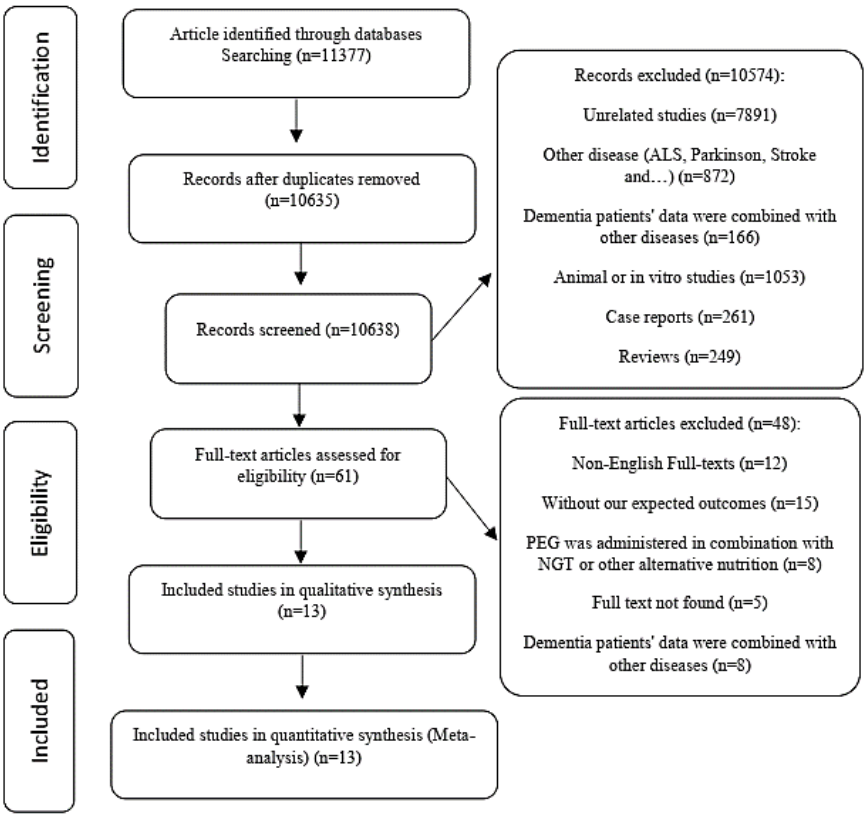

Figure 1. The Flow diagram for study selection

Study characteristics

The characteristics of included studies are presented in Table 2. Based on the search strategy in this mete-analysis, the relevant data were enrolled up to Aug 2019. A total of 1020 dementia patients had PEG feeding tube, and 1296 patients in the control group (408 demented patients with oral nutrition (ON) or NGT nutrition support, 678 patients with secondary dementia as a result of stroke with PEG, and 210 patients with other disease and PEG nutrition support) participated in the current meta-analysis. The mean age of participants was 78.5 years old. Among included studies, three studies were performed in the United States (16,19,21), three studies in Japan (24,26,27), two studies in Israel (18,22), 1 study in the United Kingdom (17), 1 study in France (20), 1 study in Sweden (23), 1 study in Colombia (25) and 1 study in Italy (28). Across the eligible articles, eight studies reported survival or mortality rate in dementia patients with PEG feeding as illustrated in Kaplan-Meier graph or table, one reported only 180-day mortality, and in 7 articles median survival days were extractable from the study texts or Kaplan-Meier graph (16-28). All of the studies were performed on both males and females except one (21). The feeding method, underlying disorder, complications, and predictors of poor survival of participants are presented in Table 2. In the four studies, the complications were not mentioned (19,23,26,28). In 8 articles, age has been evaluated as a survival predictor (17,18,20,22,23,26-28), albumin serum levels in 3 articles (18,20,27), and one articles dementia stage (21); in other included studies, various factors have been mentioned, and in two studies it has not mentioned (16,24). Six studies had prospective, and seven studies had the retrospective design. A significant increase in mortality rate in dementia patients with PEG tube feeding was reported in 3 articles (16,17,28), higher survival was observed in 3 studies (18,23,24), while Rimon *et al.*, (22),

Atencio *et al*., (25), and Ticinesi *et al*., (28) reported shorter survival in these patients. Five included articles found no significant differences in median survival in dementia patients who receive PEG in comparison to the control group (19-21,26,27) (Table 2).

Table 2. The characteristics of included studies

Author	Country	Design	Dementia group disease (n)	Control group disease (n)	intervention Dementia/ control	Gender % (M)	Age (y)	Kaplan-Meier Survival Analysis	Complication rate (n)	Predictors for Poor Survival
Nair *et al*,. 2000	USA	Pros	Dementia (55)	Other disease (33)	PEG/ON	29	82.2	Mortality at 6 months was higher in patients who had a PEG (44% vs. 26%, *P* = 0.03).	Fever (14), Cellulitis (4), Hemorrhage (1), Ileus (1)	Not mentioned
Sanders *et al*., 2000	UK	Retro	Dementia (103)	Stroke (120), Oropharyngeal malignancy (65), Miscellaneous (73)	PEG/PEG	NA	68.5	The dementia group had a worse prognosis, with a 54% mortality at 1 month,78% at 3 months, 81% at 6 months, and 90% at 1 yr.	Hemorrhage (6), Peritonitis (3), Pneumonia (97)	A Cox proportional hazards statistical analysis showed that age and group were independent predictors of mortality (*P* <0.0001).
Dwolatzky *et al*., 2001	Israel	Pros	Dementia (32)	Dementia (90)	PEG/NGT	38	82.4	PEG group was a significantly higher survival rate than those with NGT, as determined by a multivariate Cox proportional Hazard model (*P*. 0.006; HR.0.41; 95% CI, 0.22- 0.76).	The data are expressed as a hazard ratio.	Albumin (HR, 0.59; 95% CI 0.36 – 1.96) Age (HR, 1.04; 95% CI 1.01 – 1.08) Dementia (HR, 1.4; 95% CI 0.77 – 2.54)
Meier *et al*., 2001	USA	Pros	Advanced dementia (68)	Advanced dementia (31)	PEG/ON	19	84	PEG was not associated with survival (*P*. 0.9; HR.0.97; 95% CI, 0.5-1.9).	Not mentioned.	Pneumonia or urosepsis (HR, 1.9; 95% CI 1.0 – 3.6) Pressure ulcer (HR, 1.07; 95% CI 0.6 – 1.8) Dehydration or metabolic abnormality (HR, 1.6; 95% CI 0.6 – 4.3)
Paillaud *et al*., 2002	France	Retro	Dementia (33)	Without dementia (40)	PEG/PEG	32	82.6	PEG was not associated with survival between dementia patients and non-demented (*P*. 0.39).	Pneumonia (39), digestive disorders (25), stomy infection, or leakage (14), abdominal wall abscess (2), pneumoperitoneum (1).	Only patient age (*P* <0.05), patient weight (*P* <0.04), presence of pressure sores (*P* <0.001), and active infection (*P* <0.001) were found to have a significant effect on survival. Cancer, low serum albumin, dementia, underlying disease, and male gender were not identified as predictors of survival in our study

Cont. table 2

Murphy *et al*., 2003	USA	Retro	Dementia (23)	Dementia (18)	PEG/ON	100	NA	There was no statistically significant difference in survival between the groups (*P*. 0.37) using the Kaplan-Meier survival curve.	There was one major complication in the group that underwent PEG; the complication rate was 4.3%.	Despite a bleak prognosis for survival in patients with advanced dementia undergoing PEG, the alternative—no feeding—would seem worse
Rimon *et al*., 2005	Israel	Pros	Dementia (356)	Dysphagia due to stroke (362)	PEG/PEG	42	80.1	Dementia group median survival (days): (223, 95% CI, 173-309). Stroke group median survival (days): (327, 95% CI, 247-507)	Early complications (11): Infection, Peritonitis, Mortality, apnoea Late complications (176): Self-extubation, Local irritation, Leakage, Tube obstruction, Hematemesis, Buried bumper	Male (HR, 1.22; 95% CI 1.0 – 1.47) (*P*. <0.05) Feeding difficulty (HR, 1.22; 95% CI 1.0 – 1.49) (*P*. <0.05) Referral from hospital (HR, 1.44; 95% CI 1.19 – 1.74) (*P*. <0.001) Age >80 years (HR, 1.39; 95% CI 1.15 – 1.68) (*P*. <0.001)
Malmgren *et al*., 2011	Sweden	Retro	Dementia (16)	Stroke (95)	PEG/PEG	55	80.9	Patients with dementia had the the longest survival while the patients with other neurological diseases.	Not mentioned.	There was no age-related difference in the various diagnostic subgroups (data not shown)
Kumagai *et al*., 2012	Japan	Pros	Dementia (151)	Dementia (106)	PEG/NGT	53	79.2	The survival rate of the PEG group (solid line) is significantly higher by 27 months than that of the NG t group (*P*. 0.019).	Aspiration pneumonia: PEG (36, *P*. <0.01), NGT (54, *P*. 1.00)	Not mentioned.
Atencio *et al*., 2015	Colombia	Retro	Dementia (29)	Strokes and other causes (67)	PEG/PEG	39.5	77.5	patients who underwent PEG for reasons other than dementia had significantly better survival times than those who underwent PEG for reasons associated with dementia.	Serious: Buried Bumper (9), fistula (1) Minor: diarrhea, distension (31), Stoma infection (10), Bleeding (4), Changes of Feeding Tube (23)	The probability of dying after PEG is three times greater for patients whose indication for the procedure was a swallowing disorder associated with dementia (*P*. <0.001).
Ticinesi *et al*., 2016	Italy	Pros	Dementia (54)	Dementia (103)	PEG/ON	31.5	82.2	Mortality was higher in PEG than in the ON group (70% vs. 40%, *P*. < 0.001). Survival was significantly shorter in the PEG group (*P*< 0.001)	Not mentioned.	PEG feeding (HR, 1.78; 95% CI 1.07 – 2.97) (*P*= 0.02) Age (HR, 1.04; 95% CI 1.01 – 1.08) (*P*= 0.02) Type of dementia (other types vs Alzheimer's disease) (HR, 0.78; 95% CI 0.77 – 0.96) (*P*= 0.01)

Cont. table 2

Takayama *et al.*, 2017	Japan	Retro	Dementia (42)	Dementia (60)	PEG/NGT	40	75.4	A log-rank test did not show a significant difference in survival times of dementia patients with PEG tubes and those with NG tubes (P = 0.179).	Not mentioned	PEG (HR, 0.53; 95% CI 0.30 – 0.94) (P= 0.03) Age (HR, 1.04; 95% CI 1.01 – 1.07) (P= 0.008) dementia (HR, 1.80; 95% CI 0.93 – 3.45) (P= 0.07)
Tomioka *et al.*, 2017	Japan	Retro	Dementia (58)	Cerebrovascular disorder (34)	PEG/PEG	63	80.7	A log-rank test did not show a significant difference in survival times of dementia patients with PEG tubes and other diseases (P = 0.65).	Aspiration pneumonia: Dementia (7, P= 0.084), CVD (9, P= 0.084)	Adjusted HR: Age (HR, 1.06; 95% CI 1.01 – 1.12) (P= 0.029) Albumin (HR, 0.36; 95% CI 0.16 – 0.83) (P= 0.017)

Pros, prospective; Retro, retrospective; HR, hazard ratio; CI, confidence interval; NA, not applicable; PEG, percutaneous endoscopic gastrostomy; ON, Oral Nutrition; NGT, nasogastric tube; CVD, Cerebrovascular disorder.

The 30-day mortality in demented patients with PEG

As presented in (Figure 2), the risk ratio performed on eight studies showed PEG intervention had no statistically significant effect on 30-day mortality (RR: 1.16; 95% CI: 0.59 to 2.28; P=0.66). In addition, significant heterogeneity was observed among studies (I^2=81%, P<0.001).

To identify the between-study heterogeneity sources, subgroup analysis was conducted on control group intervention (oral, NGT, or PEG), diseases, and age (Table 3). The subgroup analysis found that in 30-day mortality, the PEG method intervention in the control group, as well as disease (dementia or other disorder), and 80>age was detected as the potential sources of heterogeneity. However, among these subgroups, no significant reduction in 30-day mortality was found after subgroup analysis based on feeding method, disease, and age (Table 3).

The 90-day mortality in demented patients with PEG

The overall risk ratio (RR) from 8 studies showed that PEG intervention exerts no significant reduction in 90-year mortality (RR: 1.13; 95% CI: 0.60 to 2.16; P=0.70), with a considerable between studies heterogeneity (I^2=93%, P<0.001) (Figure 3). Subgroup analysis showed that PEG intervention in the control group, disease (dementia or other diseases), and age (80> or 80≤) are considered as heterogeneity sources. Following subgroup analysis based on feeding route in control participants, a significant reduction in 90-day mortality was found in the NGT group (RR: 0.51; 95% CI: 0.31 to 0.82; P=0.005) and increasing in 90-day mortality in oral feeding in (RR: 1.70; 95% CI: 1.06 to 2.74; P=0.03) comparison with PEG receiving patients with dementia.

In addition, no significant differences in 90-day mortality were observed after subgroup analysis based on other diseases or age (Table 3).

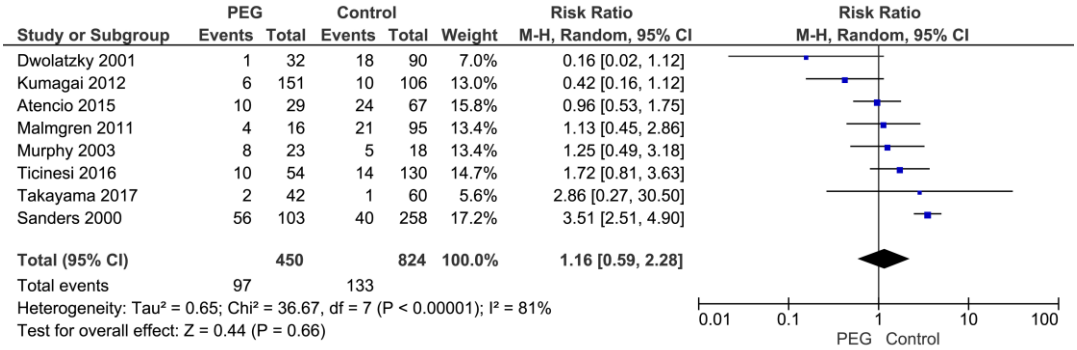

Figure 2. 30-day mortality rate in demented patients with PEG feeding

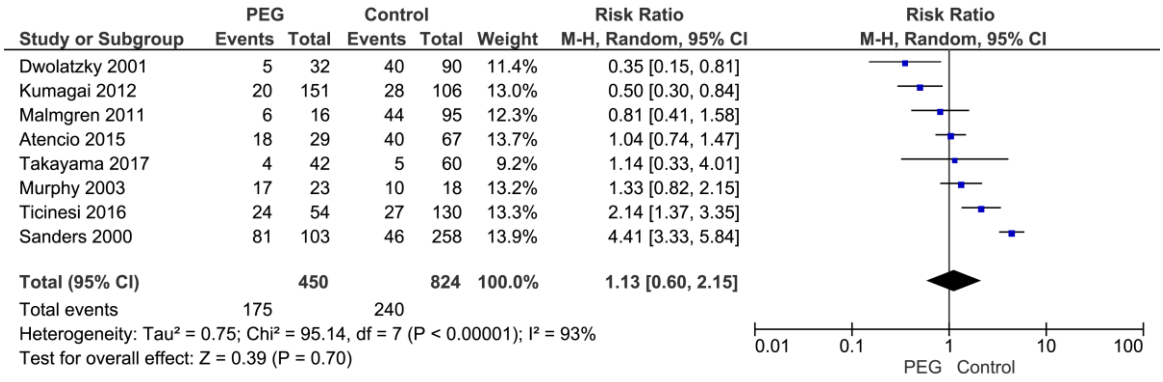

Figure 3. 90-day mortality rate in demented patients with PEG feeding

Table 3. Subgroup analysis of mortality rate

Subgroup heading	Outcome of interests	Subgroups	Number of studies	RR (95% CI)	*P*	Heterogeneity		
						χ2	I2, %	*P*
Control group intervention	30-days mortality	NGT	3	0.48(0.13, 1.76)	0.27	3.54	43	0.17
		Oral	2	1.52(0.85, 2.72)	0.16	0.27	0	0.60
		PEG	3	1.63(0.62, 4.31)	0.32	16.51	88	<0.001
	90-days mortality	NGT	3	0.51(0.31, 0.82)	0.005	2.36	15	0.31
		Oral	2	1.70(1.06, 2.74)	0.03	2.11	53	0.15
		PEG	3	1.58(0.51, 4.95)	0.43	50.66	96	<0.001
	180-days mortality	NGT	3	0.59(0.43, 0.81)	0.001	2.19	9	0.34
		Oral	3	1.58(0.96, 2.60)	0.07	8.26	76	0.02
		PEG	3	1.15(0.64, 2.07)	0.65	25.47	92	<0.001
	1-year mortality	NGT	3	0.67(0.46, 0.97)	0.04	4.54	56	0.10
		Oral	2	1.39(0.61 3.19)	0.44	25.33	96	<0.001
		PEG	3	1.11(0.65, 1.91)	0.69	62.73	97	<0.001
	2-years mortality	NGT	2	0.63(0.50, 0.79)	<0.001	0.05	0	0.82
		Oral	1	1.46(1.21, 1.75)	<0.001	-	-	-
		PEG	2	1.22(0.67, 2.23)	051	136.9	99	<0.001
Control group disease	30-days mortality	Dementia	5	0.88(0.38, 2.04)	0.77	10.00	60	0.04
		Other diseases	3	1.63(0.62, 4.31)	0.32	16.51	88	<0.001
	90-days mortality	Dementia	5	0.91(0.45, 1.86)	0.80	26.52	85	<0.001
		Other diseases	3	1.58(0.51, 4.95)	0.43	50.66	96	<0.001
	180-days mortality	Dementia	5	0.92(0.55, 1.55)	0.76	28.92	86	<0.001
		Other diseases	4	1.29(0.78, 2.14)	0.32	26.29	89	<0.001
	1-year mortality	Dementia	5	0.94(0.60, 1.46)	0.78	40.02	90	<0.001
		Other diseases	3	1.11(0.65, 1.91)	0.69	62.37	97	<0.001
	2-years mortality	Dementia	3	0.85(0.43, 1.69)	0.64	37.15	95	<0.001
		Other diseases	2	1.22(0.67, 2.23)	0.51	136.9	99	<0.001
Age (years)	30-days mortality	80≤	3	0.93(0.32, 2.71)	0.89	5.80	65	0.06
		80>	5	1.33(0.54, 3.27)	0.54	27.50	85	<0.001
	90-days mortality	80≤	3	0.89(0.30, 2.58)	0.82	16.88	88	<0.001
		80>	5	1.31(0.55, 3.11)	0.54	74.35	95	<0.001
	180-days mortality	80≤	3	0.91(0.37, 2.23)	0.83	19.30	90	<0.001
		80>	6	1.15(0.76, 1.74)	0.52	46.10	89	<0.001
	1-year mortality	80≤	3	0.97(0.46, 2.06)	0.94	24.26	92	<0.001
		80>	5	1.03(0.74, 1.43)	0.88	66.97	94	<0.001
	2-years mortality	80≤	1	1.46(1.21, 1.75)	<0.001	-	-	-
		80>	4	0.92(0.67, 1.27)	0.62	83.37	96	<0.001

The 180-day mortality in demented patients with PEG

According to (Figure 4) illustrated RR of PEG feeding on 180-day mortality rate in patients with dementia performed on nine studies (505 cases and 857 controls), PEG intervention exerts no statistically significant reduction on 180-day mortality rate (RR: 1.07; 95% CI: 0.75 to 1.53; *P*=0.70). There was significant heterogeneity among included studies (I^2=88%, *P*<0.001). Following subgroup analysis based on feeding route, disease, and age as identified heterogeneity sources, a significant reduction in 180-day mortality was observed in NGT receiving group (RR: 0.59; 95% CI: 0.43 to 0.81; *P*=0.001) comparison with PEG intervention in patients with dementia. Also, no significant differences in 180-day mortality were found

after subgroup analysis based on other diseases or age (Table 3).

The 1-year mortality in demented patients with PEG

At the present meta-analysis, based on overall effect sizes of 8 included data, the PEG intervention had no significant effect on 1-year mortality reduction (RR: 1.01; 95% CI: 0.77 to 1.33; *P*=0.94), with considerable heterogeneity across enrolled studies (I^2=92%, *P*<0.001) (Figure 5). After subgroup analysis, a significant reduction in 1-year mortality rate was detected in the NGT receiving group (RR: 0.67; 95% CI: 0.46 to 0.97; *P*=0.04) comparison with PEG intervention in dementia patients (Table 3).

The 2-year mortality in demented patients with PEG

The overall effect sizes performed on five studies illustrated that PEG intervention couldn't exert any statistically significant differences on 2-year mortality rate in patients with dementia (RR: 1.02; 95% CI: 0.77 to 1.34; *P*=0.91) (Figure 6). As presented in figure 6, significant between-studies heterogeneity was detected (I^2=96%, *P*<0.001). After subgroup analysis, a significant reduction in 2-year mortality rate was detected in the NGT receiving group (RR: 0.63; 95% CI: 0.50 to 0.79; *P*<0.001) comparison with PEG intervention in dementia patients (Table 3). In addition, in patients 80≤years, PEG intervention significantly increases 2-year mortality (RR: 1.46; 95% CI: 1.21 to 1.75; *P*<0.001).

The median survival days in demented patients with PEG

Figure 7 illustrates the WMD of median survival days in demented patients with the PEG method. The overall effect of the random-effect model that was performed on seven studies showed PEG intervention had no statistically significant effect on patient's median survival (WMD: 9.77; 95% CI: -22.43 to 41.98; *P*=0.55) (Figure 7). In addition, no significant between studies heterogeneity was identified among included studies (I^2=0%, *P*=0.48) (Table 4).

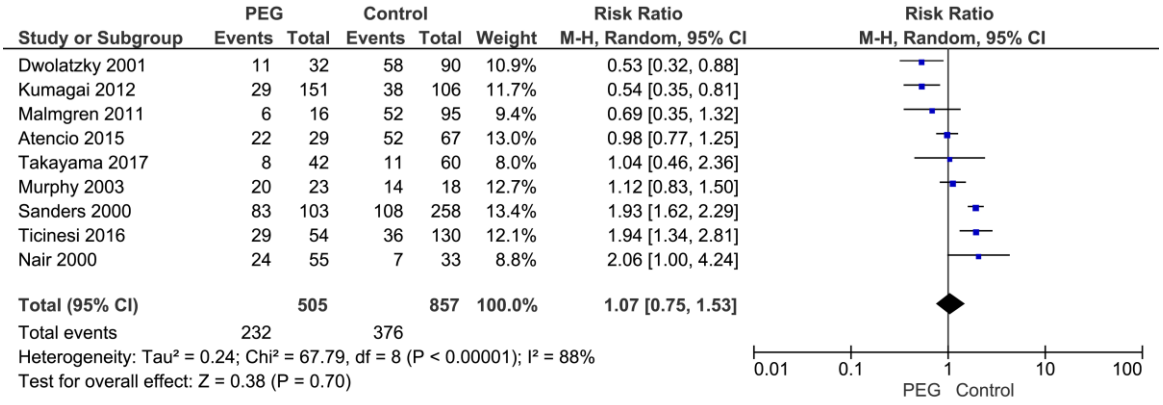

Figure 4. 180-day mortality rate in demented patients with PEG feeding

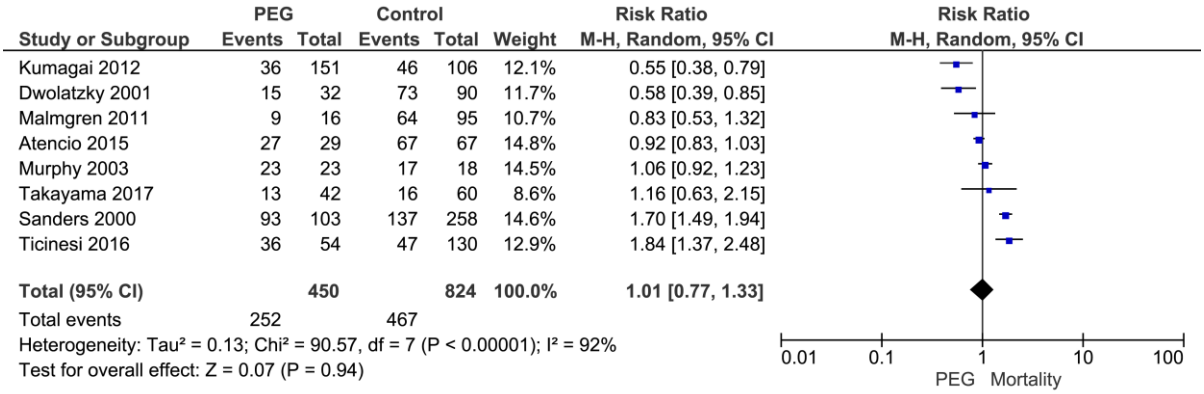

Figure 5. 1-year mortality rate in demented patients with PEG feeding

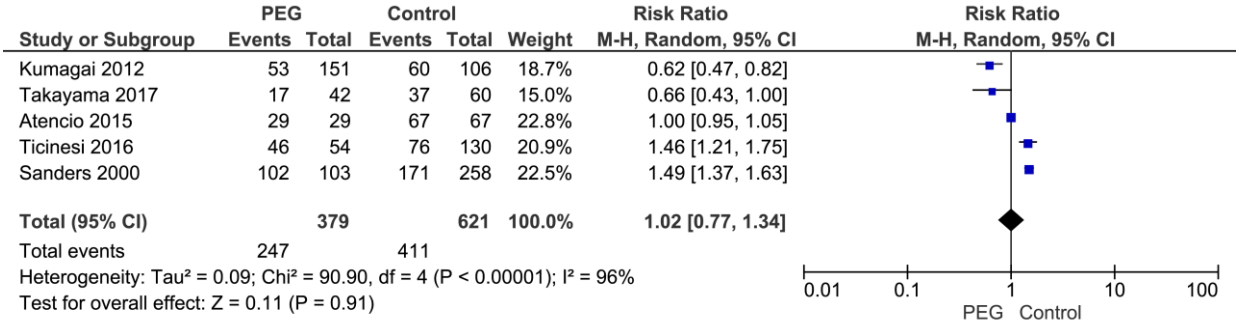

Figure 6. 2-year mortality rate in demented patients with PEG feeding

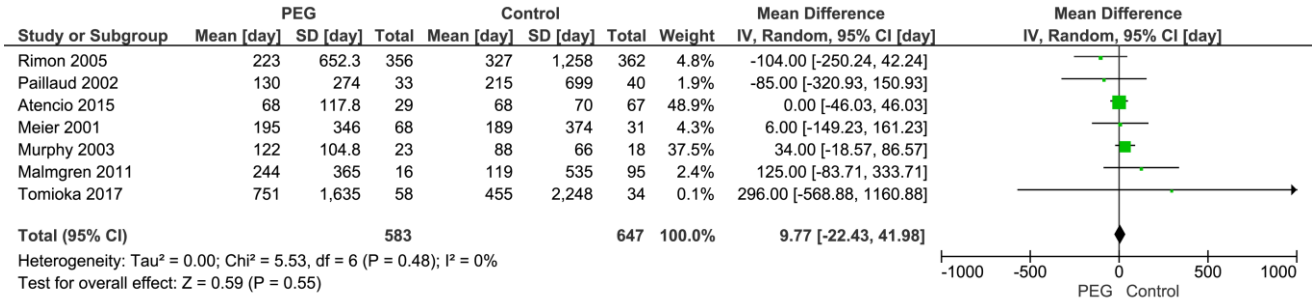

Figure 7. Median survival in demented patients with PEG feeding

Table 4. Subgroup analysis of median survival

Subgroup heading	Subgroups	Number of studies	WMD (95% CI)	*P*	Heterogeneity		
					χ2	I2, %	*P*
Control group disease	Oral	2	31.12(-18.7, 80.9)	0.22	0.11	0	0.74
	PEG	5	-7.63(-58.9, 43.7)	0.77	1.20	5	0.38
	Dementia	3	26.17(-22.5, 74.9)	0.29	1.00	0	0.61
	Other diseases	4	-4.88(-78.8, 69.0)	0.90	3.75	20	0.29
Age (years)	80≤	5	-21.8 (-109.9, 66.2)	0.63	4.03	1	0.40
	80>	2	14.75(-19.9, 49.4)	0.40	0.91	0	0.34
Total	-	7	9.77(-22.4, 41.9)	9.77	5.53	0	0.48

Discussion

The current systematic review and meta-analysis included 13 studies and a total of 1020 participants in the PEG group with dementia and 1296 participants in the control group. The PEG intervention has no statistically significant effect on 30-day, 90-day, 180-day, 1-year, and 2-year mortality rates or median survival days in patients with dementia. In addition, in order to clarify the effect of the PEG feeding method on mortality rate and survival in dementia patients, subgroup analyzes were performed based on age as 80> or 80≤, control group disorders as dementia or other disease and feeding method in the control group as oral, NGT or PEG. However, after subgroup analysis, it is found that NGT intervention in compared to PEG in dementia patients can significantly reduce 90-day, 180-day, 1-year, and 2-year mortality rates while oral intake significantly increased 90-day and 2-year mortality rates. Also, 2-year mortality significantly increased in patients 80≤years old.

The PEG has been considered as a long-term enteral feeding since the 1980s, which can reduce the aspiration rate in comparison to NGT can be used in patients who are expected to require enteral feeding for more than 2-3 weeks (29,30). On the basis of pieces of evidence, PEG insertion can increase serum albumin that accounts for a biomarker of nutritional status evaluation (31). The PEG method is well accepted in patients with neurological diseases who have nutritional difficulties such as dysphagia (32). But PEG placement in dementia patients is conflicting. Dementia is usually associated with major nutritional problems such as eating, chewing, swallowing, etc., especially with the progression of the disease, which leads to inadequate intake, weight loss, and serious malnutrition (2). So, these patients often need support nutrition. Despite contradictory pieces of evidence, at the moment, PEG

insertion is prescribed by physicians in the majority of dementia cases since they can't intake adequate energy and proteins, which may affect dementia progression (33).

In the current systematic review and meta-analysis, in dementia patients, PEG intervention could not affect mortality rate at any time and even increased mortality risk ratio, although it was not statistically significant. These findings are parallel with the results of several trials, which reported that the mortality rate significantly increased in PEG receiving patients with dementia (16,28). In this context, Sanders *et al*., demonstrated that dementia patients with PEG had a lower prognosis, with a 54% mortality at 30-day,78% at 90-day, 81% at 180-day, and 90% at one-year (17). Also, similar to mortality results, the PEG insertion in dementia patients had exerted no significant positive differences in median survival. Most of the previous studies in the context of PEG intervention and survival confirm the present results (26,27). Some studies found no association between PEG insertion and survival in dementia patients (19,21), while Ticinesi *et al.,* (2016) and Atencio *et al*., (2015) reported a significantly shorter survival in the PEG group with dementia (25,28). In contrast, a significant positive effect of PEG insertion on increasing survival in dementia patients has been demonstrated (18). However, the most of the prospective studies the PEG enteral nutrition is not associated with an improvement in nutritional status, course of the disease, or survival (6). In this context, Teno *et al*., in their large prospective cohort study in patients with dementia, found no correlation between PEG and survival (34). Even, PEG method may be associated with a higher risk of pressure ulcers as secondary adverse effects (35). Also, in other disorder with nutritional problems such as Amyotrophic lateral sclerosis, no significant improvement in mortality or survival were observed (36).

In the current meta-analysis, we observed that NGT in compared to PEG in dementia patients could significantly reduce the mortality rate. Although the results of studies in this area are conflicting, the majority of pieces of evidence did not observe significant effects on mortality or survival (18). A meta-analysis by Elke *et al*., (2016) reported that in critically ill patients, the NGT had no effect on mortality rate but could decrease comorbidities (such as infectious complications or mechanical ventilation (37). Another study also reported that the PEG insertion is more effective and safer compared to NGT, but no significant difference in mortality rates or adverse outcomes was observed (38). It seems that mortality or survival may depend more on the nature and stage of disease, comorbidities, and performance status, which still poorly have been investigated (39).

In addition, our subgroup analysis found 80≤ age as a strong predictor of 2-year mortality, which is contrary to Ticinesi *et al*., results (28). Parallel with this; it has been observed that PEG insertion in patients before the age of 80 had significantly longer survival than others (40,41). However, further studies are needed to reach a definitive conclusion in this case. In this regard, to evaluate the effect of PEG feeding on mortality and survival and make a correct decision to apply in patients with dementia, further comprehensive evaluation of comorbidities, underlying disease, lifestyle, cognitive and physical performance as well as nutritional problems should be conducted in older patients with advanced or not-advanced dementia.

The main limitation of the present study was that the control group was not homogeneous in terms of underlying diseases, and the feeding method was adjusted by subgrouping analysis. Another limitation was the limited number of studies in primary dementia conditions. The majority of studies were performed in patients with secondary dementia derived from stroke or another disease. In addition, the stage of dementia was not mentioned in many studies, which exerts a considerable effect on the prognosis of the disease.

In conclusion, the present systematic review and meta-analysis showed that PEG insertion in patients with primary dementia has no significant effect on mortality rates or median survival. It seems that NGT feeding in compared to PEG in this population is more effective in the context of reduction of mortality rate. Larger human studies considering clinical, paraclinical, and nutritional status as well as disease stage, etc., should be performed in primary dementia patients to clarify whether a PEG feeding method can be effective in reducing mortality and increasing survival.

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