Original Article

Prognostic Outcome of Pulmonary Resection for Pulmonary Metastases from Gastric Cancer

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Purpose: Regardless of the devastating outcomes of pulmonary resection for metastases from gastric cancer, a handful of patients survive long after pulmonary metastasectomy. This study aimed to identify a good candidate for pulmonary resection for metastases from gastric cancer.

Methods: Between 2005 and 2023, 564 patients underwent pulmonary metastasectomy in our department, of which 12 patients underwent pulmonary resection for metastases from gastric cancer. Variables evaluated were the number and size of metastatic lesions, surgical procedure, disease-free interval (DFI), and the serum carcinoembryonic antigen at pulmonary metastasectomy.

Results: The DFI following gastrectomy ≤12.5 months group had a significantly worse overall survival (OS) than the other group (p = 0.005). A comparison between DFI following gastrectomy ≤12.5 months group and DFI following gastrectomy >12.5 months group showed a significant difference in serum carcinoembryonic antigen (CEA) value at pulmonary metastasectomy (p = 0.048). The serum CEA value at pulmonary metastasectomy >5.8 ng/ml group had a significantly worse OS than the other group (p = 0.001).

Conclusion: Pulmonary metastasectomy can be indicated in some patients with metastasis from gastric cancer who have longer DFI from gastrectomy and lower serum CEA at pulmonary metastasectomy.

Keywords: gastric cancer, gastrectomy, pulmonary metastases, pulmonary metastasectomy

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Introduction

Gastric cancer is a common cancer among Japanese people, ranking third in the incidence rate and third in the mortality rate. Recurrence patterns of gastric cancer include peritoneal recurrence, hematogenous metastases to the liver, and localized lymph node recurrence. It is extremely rare for pulmonary metastases from gastric cancer to be eligible for pulmonary resection.[1–3] In general, many digestive tract cancers cause hematogenous metastases to the lungs, and over the years, eligibility for pulmonary metastases has been determined according to the Thomford's criteria.[4] Surgical eligibility guidelines for pulmonary metastases from many solid cancers, with the exception of gastric cancer, were established based on accumulated data.[5–10]

There are some case reports[11,12] of successful long-term outcomes of pulmonary resection for metastases from gastric cancer. However, there have been very few observational studies that have shown surgical outcomes of patients with pulmonary metastasis from gastric cancer.[1–3,13–17] Several reports[13,16] have shown that patients with long disease-free intervals (DFI) following gastrectomy are good candidates for pulmonary metastasectomy. Unfortunately, eligibility criteria for pulmonary resection for metastasis from gastric cancer are not still established because some of the important clinical information is lacking in these studies, such as whether or not chemotherapy before pulmonary metastasectomy is performed,[10,11,13] whether or not extrapulmonary metastases are controlled,[11] and whether or not the pulmonary metastasis is solitary.[1]

We aimed to clarify factors associated with the prognosis of patients undergoing pulmonary resection for metastatic gastric cancer to discuss selection criteria for the surgical treatment.

Materials and Methods

Study design and participants

During the period from May 1, 2005 to March 31, 2023, we underwent 564 pulmonary resections for pulmonary metastases at our department. Among them, there were 12 patients with pulmonary metastases from gastric cancer. In this study, all patients included were metachronous pulmonary metastases. Case numbers in the table are in chronological order of pulmonary metastasectomy. Regarding surgical indications, we basically followed Thomford's criteria.[4] However, according to Thomford's criteria, surgery is not applicable if there are bilateral pulmonary lesions. However, recently, the use of thoracoscopy has made the surgery less invasive, so pulmonary metastasectomy is often indicated for bilateral lesions. Therefore, we evaluated 12 patients with pulmonary resection for metastatic gastric cancer, including two patients who had bilateral lesions. Pulmonary metastasectomy was indicated when the primary cancer and metastatic lesions outside the lung were under control, and there was no effective treatment except for surgery.

The 8th edition of the UICC TNM classification was used for the tumor staging, and the tumor depth and presence/absence of node metastases were considered.[18] Histology was defined as papillary (pap), tubular (tub), poorly differentiated (por) adenocarcinoma, or others. Both the gastrectomy and lymph node dissection were carried out based on the Japanese Gastric Cancer Treatment Guidelines 2010 (version 3).[19]

This retrospective clinical study was approved by the Kagoshima University Hospital Ethics Committee (Research approval number: 230087). Research participants and their relatives could opt out by viewing the research content hosted online.

Statistical analysis

The value of DFI following gastrectomy in diagnosing survival was evaluated by receiver operating characteristic (ROC) analysis, and the cutoff value was defined by selecting the point on the ROC curve with the minimum distance from the left upper corner of the unit square.

Overall survival (OS) was defined as the interval from the day of pulmonary metastasectomy until the date of death from any cause, censored for patients who were alive at the last clinic visit.

Patient survival curves were plotted using the Kaplan–Meier method, and the difference between the curves of groups was analyzed using the log-rank test. To select significant factors, the Mann–Whitney U test and Fisher's exact test were used to compare each factor between the DFI following gastrectomy ≤12.5 months group and the DFI following gastrectomy >12.5 months group. The serum carcinoembryonic antigen (CEA) value at pulmonary metastasectomy on diagnosing DFI following gastrectomy was evaluated by ROC analysis, and the cutoff value was defined by selecting the point on the ROC curve with the minimum distance from the left-upper corner of the unit square.

All statistical analyses were performed with EZR software (Saitama Medical Center, Jichi Medical University, Saitama, Japan) and SPSS (Dr. SPSS II for Windows, Standard Version 26.0; SPSS, Inc, Chicago, IL, USA). A p-value of less than 0.05 was considered to be significant.

Results

The clinical characteristics of 12 patients with gastrectomy are shown in **Table 1**. There were 10 males and 2 females. Eight patients underwent total gastrectomy, three patients underwent proximal gastrectomy, and one patient underwent distal gastrectomy for gastric cancer. Three patients received preoperative chemotherapy before gastrectomy.

Clinical features and postoperative outcomes of 12 patients with pulmonary metastasectomy are shown in

Table 1 Clinical characteristics of 12 patients at gastrectomy

No	Age	Gender	Serum CEA	SUV max	Preoperative chemotherapy	Surgical procedure	Pathological stage	Histological type	Adjuvant chemotherapy
1	69	M	12.5	NA	(-)	TG	pIV	tub	(+)
2	66	M	16.1	NA	(-)	TG	pIIIA	tub	(+)
3	76	M	11.3	11.0	(-)	TG	pIIB	tub	(-)
4	58	M	4.9	23.8	(-)	PG	pIIA	tub	(-)
5	73	M	1.4	NA	(-)	TG	pIB	tub	(-)
6	63	M	10.4	11.5	(+)	TG	ypIIA	tub	(+)
7	70	M	6.0	16.9	(+)	PG	ypIB	tub	(+)
8	63	M	2.0	NA	(-)	TG	pIB	tub	(-)
9	80	F	8.1	NA	(-)	TG	pIIB	tub	(-)
10	80	M	5.0	18.9	(+)	TG	ypIIA	tub	(-)
11	67	M	3.1	5.31	(-)	DG	pIA	por	(-)
12	74	F	12.2	9.49	(-)	PG	pIIA	tub	(-)

CEA: carcinoembryonic antigen; SUV: standardized uptake value; M: male; F: female; NA: not available; TG: total gastrectomy; DG: distal gastrectomy; PG: proximal gastrectomy

Table 2. After gastrectomy, one patient developed liver metastasis, and three patients developed intra-abdominal lymph node metastasis. However, these were locally controlled with resection or radiotherapy. The median DFI following gastrectomy was 16.7 months (range: 5.7–48.9 months). Four patients underwent lobectomy, seven patients underwent wedge resection, and one patient underwent lobectomy and wedge resection for pulmonary metastases. Four patients received preoperative chemotherapy before pulmonary metastasectomy. Five patients developed intraperitoneal lymph node metastases, one patient developed liver metastasis, and one patient developed pulmonary metastasis and lymph node metastases after pulmonary metastasectomy. The median OS following pulmonary metastasectomy was 23.1 months (range: 4.9–74.1 months). Five of the 12 patients died during the follow-up period due to gastric cancer.

According to ROC curves showing the diagnostic potential of DFI following gastrectomy on survival of 12 patients, the best cutoff value was 12.5 months (sensitivity: 80.0%, specificity: 85.7%, area under the curve (AUC): 0.857, 95% CI: 0.618–1.000) (**Fig. 1A**): 12 patients can be divided into two groups, as patients with DFI following gastrectomy ≤12.5 months (n = 5) and patients with DFI following gastrectomy >12.5 months (n = 7). The patients with DFI ≤12.5 months after gastrectomy had a worse OS following pulmonary metastasectomy than the others (p = 0.005) (**Fig. 1A**).

Table 3 shows differences in clinical characters between patients with DFI following gastrectomy ≤12.5 months and those with DFI following gastrectomy ≤12.5 months: significant differences were observed regarding serum CEA value at pulmonary metastasectomy (p = 0.04) and observation period (p = 0.005) (**Table 3**). According to ROC curves showing the diagnostic potential of serum CEA value at pulmonary metastasectomy on longer DFI following gastrectomy (>12.5 months), the best cutoff value of serum CEA value was 5.8 ng/ml (sensitivity: 85.7%, specificity: 80.0%, AUC: 0.857, 95% CI: 0.632–1.000) (**Fig. 2A**): 12 patients can be divided into two groups, as patients with serum CEA value at pulmonary metastasectomy ≤5.8 (n = 7) and patients with serum CEA value at pulmonary metastasectomy >5.8 (n = 5). The patients with serum CEA value at pulmonary metastasectomy >5.8 had a worse OS following pulmonary metastasectomy than the others (p = 0.001) (**Fig. 2B**). The prognosis of 12 patients during the observation period is shown using the DFI following gastrectomy ≤12.5 months and the serum CEA value at pulmonary metastasectomy >5.8 as risk factors (**Table 4**). Five of the six patients with either risk factor died during the observation period.

Discussion

The current study revealed that DFI following gastrectomy and serum CEA value at pulmonary metastasectomy were factors related to OS after pulmonary resection for metastatic gastric cancer. The cutoff values for DFI and serum CEA value were determined by ROC analysis, which accurately reflected survival outcomes.

Table 2 Clinical features and outcome of pulmonary metastases

No	Largest tumor size on CT (mm)	Number of lesions	Serum CEA	DFI (months)	SUV max	Other metastatic organs	Preoperative chemotherapy	Surgical procedure	Postpulmonary metastasectomy course	OS (months)	Status
1	12	2 (hemilateral)	8.6	10.1	12.2	Lymph node	(+)	Lobectomy	Lung/LN recurrence	14.5	Dead
2	10	1	10.9	17.0	2.3	Lymph node	(+)	Wedge	LN recurrence	22.0	Dead
3	6	2 (bilateral)	14.7	5.7	2.1		(–)	Wedge	LN recurrence	19.3	Dead
4	31	1	1.9	38.3	3.79		(–)	Lobectomy		74.1	Alive
5	20	1	4.2	12.5	7.4		(+)	Wedge	Liver recurrence	24.2	Dead
6	15	1	2.6	25.3	14.9	Lymph node	(–)	Wedge		40.2	Alive
7	10	1	6.3	10.2	5.67	Liver	(+)	Wedge	LN recurrence	13.5	Dead
8	15	1	2.7	48.9	11.4		(–)	Lobectomy		44.8	Alive
9	20	3 (bilateral)	4.5	24.6	12.0		(–)	Lobectomy + wedge	LN recurrence	43.9	Alive
10	25	2 (hemilateral)	3.8	16.4	19.5		(–)	Lobectomy	LN recurrence	12.2	Alive
11	7	1	5.8	36.0	11.4		(–)	Wedge		35.3	Alive
12	5	1	11.6	9.4	0.47		(–)	Wedge		4.9	Alive

CT: computed tomography; CEA: carcinoembryonic antigen; SUV: standardized uptake value; OS: overall survival; Wedge: wedge resection; LN: lymph node

In our study, all six patients with DFI longer than the cutoff value and CEA value lower than the cutoff value survived throughout the follow-up period. Five out of six patients with DFI following gastrectomy ≤12.5 months and/or serum CEA value at pulmonary metastasectomy >5.8 ng/ml died during the observation period. The median OS following pulmonary metastasectomy was 16.9 months (range: 4.9–24.2 months). The remaining patient (Case No. 12) living with both factors had the shortest follow-up period (4.9 months) (**Table 4**). Therefore, surgery cannot be actively recommended in this population.

Most of the clinical reports on pulmonary resection for metastatic gastric cancer are derived from Japan. Shiono et al. reported the largest sample size (n = 51) based on the Metastatic Lung Tumor Study Group database of Japan.[13] They concluded that patients with a DFI of 12 months or more following gastrectomy are good candidates for pulmonary resection for metastases, which supports our findings. However, there was no clinical information regarding tumor markers in that study. In the current study, we proposed that patients with higher CEA values at pulmonary metastasectomy may have a poor prognosis.

Preoperative serum CEA value is considered to be a prognostic factor for patients undergoing gastrectomy for gastric cancer.[20] In our study, higher serum CEA value at pulmonary resection for metastases from gastric cancer was also associated with poor postoperative prognosis. However, it cannot be determined from our study whether the serum CEA value at pulmonary metastasectomy and DFI following gastrectomy are independent prognostic factors because these can be confounding factors. Nonetheless, it is possible that elevated serum CEA value at pulmonary metastasectomy is caused not only by pulmonary metastases but also by subclinical micrometastases in other organs.

On the other hand, neither the number of pulmonary metastases ($p = 0.922$) nor the surgical procedure (lober/sublobar resection) ($p = 0.565$) was associated with survival outcomes in our study. However, those are generally the prognostic factors in patients with pulmonary metastasis from digestive tract cancers.[21–23] Our study results suggested that prognostic factors of patients with pulmonary metastases from gastric cancer differ from those with other digestive tract cancers, suggesting that specific surgical eligibility criteria should be defined for pulmonary metastasis from gastric cancer.

In the current study, some patients received chemotherapy before and/or after gastrectomy and/or before

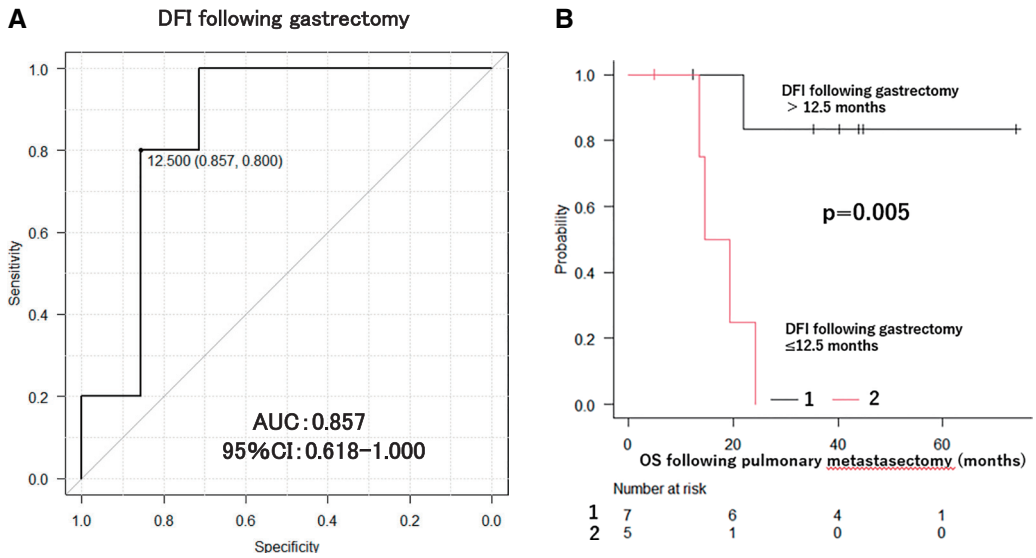

Fig. 1 ROC curves for 12 patients who underwent pulmonary resection for metastases from gastric cancer. The diagnostic potential of DFI following gastrectomy was evaluated by ROC analysis (**A**). Overall survival curves following pulmonary metastasectomy for 12 patients who underwent pulmonary resection for metastases from gastric cancer. The 12 patients were divided into two groups: DFI following gastrectomy ≤12.5 months and DFI following gastrectomy >12.5 months (**B**). DFI: disease-free interval; ROC: receiver operating characteristic

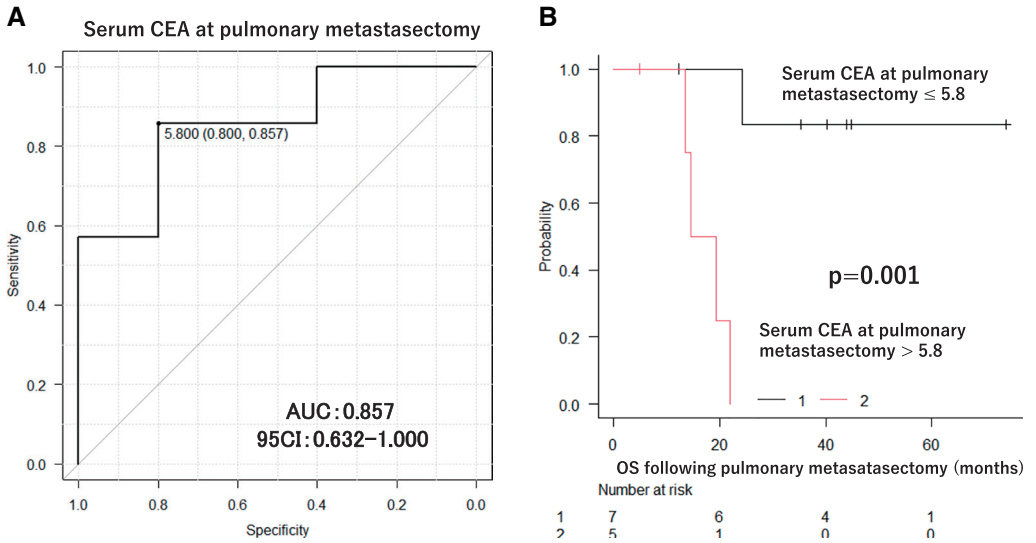

Fig. 2 ROC curves for 12 patients who underwent pulmonary resection for metastases from gastric cancer. The diagnostic potential of serum CEA at pulmonary metastasectomy was evaluated by ROC analysis (**A**). Overall survival curves following pulmonary metastasectomy for 12 patients who underwent pulmonary resection for metastases from gastric cancer. The 12 patients were divided into two groups: serum CEA value at pulmonary metastasectomy ≤5.8 and serum CEA value at pulmonary metastasectomy >5.8 (**B**). CEA: carcinoembryonic antigen; ROC: receiver operating characteristic

pulmonary metastasectomy. For locoregional gastric cancer, perioperative chemotherapy, including preoperative chemotherapy, is an option.[24] Three patients received neoadjuvant chemotherapy before gastrectomy. Although the CEA value decreased in two out of three patients, all three patients, including these two patients, developed lung metastasis. Moreover, preoperative chemotherapy before gastrectomy had no effect on DFI following gastrectomy.

Table 3 Nonparametric test between DFI following gastrectomy ≤12.5 group and DFI following gastrectomy >12.5 months group

Clinical characteristics	DFI ≤12.5 months (n = 5)	DFI >12.5 months (n = 7)	p-value
Age at gastrectomy (years)	Median 73 (range: 69–76)	Median 66 (range: 58–80)	0.254
Gender (female/male)	1/4	1/6	1.00
Serum CEA value at gastrectomy (ng/ml)	Median 11.3 (range: 1.4–12.5)	Median 5.0 (range: 2.0–16.1)	0.53
Preoperative chemotherapy before gastrectomy			
Not enforced/done	4/1	5/2	1.00
Type of gastrectomy			
Total/distal/proximal gastrectomy	3/0/2	5/1/1	0.735
Pathological stage (including preoperative chemotherapy)			
pIA/pIB(ypIB)/pIIA(ypIIA)/pIIB/pIIIA /pIV	3/2/0/0/0/0	1/1/3/1/1/0	0.818
Maximum pulmonary tumor size (mm)	Median 10 (range: 5–20)	Median 15 (range: 7–31)	0.142
Adjuvant chemotherapy after gastrectomy			
Not enforced/done	3/2	5/2	1.00
Number of pulmonary lesions	Median 1 (range: 1–2)	Median 1 (range: 1–3)	0.922
Serum CEA level at pulmonary metastasectomy (ng/ml)	Median 8.6 (range: 4.2–14.7)	Median 3.8 (range: 1.9–10.9)	0.048
SUV max at pulmonary lesions	Median 5.67 (range: 0.47–12.2)	Median 11.4 (range: 2.30–19.5)	0.193
Preoperative chemotherapy before pulmonary metastasectomy			
Not enforced/done	2/3	6/1	0.222
Surgical procedure of pulmonary metastasectomy			
Wedge/lobectomy	4/1	4/4*	0.565
Observation period (months)	Median 31.8 (range: 18.9–45.8)	Median 76.3 (range: 33.8–118.8)	0.005

*One patient underwent both wedge and lobar resection. CEA: carcinoembryonic antigen; CT: computed tomography; SUV: standardized uptake value

Table 4 Outcome of patients with/without prognostic factors

No	DFI following gastrectomy ≤12.5 months	Serum CEA at pulmonary metastasectomy >5.8	Status
1	●	●	Dead
2	○	●	Dead
3	●	●	Dead
4	○	○	Alive
5	●	○	Dead
6	○	○	Alive
7	●	●	Dead
8	○	○	Alive
9	○	○	Alive
10	○	○	Alive
11	○	○	Alive
12	●	●	Alive

●: higher risk; ○: lower risk

Conventionally, postoperative fluoropyrimidine-based adjuvant chemotherapy for gastric cancer has been recommended.[24] However, adjuvant chemotherapy was not associated with DFI following gastrectomy. In the current study, the number of cases enrolled in this study was small, and all of the cases were patients with gastric cancer recurrence, including lung metastasis, so it was not possible to accurately evaluate the effectiveness of perioperative chemotherapy for gastric cancer.

In the current study, four patients received chemotherapy before pulmonary metastasectomy. Three of the four patients had metastases to other organs. One patient had liver metastasis, and two patients had intra-abdominal lymph node metastasis. These were locally controlled with resection or radiotherapy and underwent pulmonary metastasectomy. However, all three patients eventually recurred in other organs and died during the observation period. This suggests that chemotherapy with cytotoxic anticancer drugs followed by lung metastasectomy is not a curative treatment for patients with recurrence in multiple organs, even if metastatic lesions in organs other than the lung are controlled with local therapy. The systemic therapy containing immune checkpoint inhibitors is expected to be effective in such cases.[24] No patients were treated with immune checkpoint inhibitors (ICIs) during the current study period. Moreover, because three of the four patients who received chemotherapy before pulmonary metastasectomy had metastasis to other organs, it is difficult to evaluate the pros and cons of chemotherapy before resection of localized metastasis of gastric cancer due to selection bias. This point needs to be evaluated in multicenter randomized controlled trials.

Our study subjected only small samples, which may have resulted in a limitation. The reported incidence of pulmonary resection for metastases from gastric cancer is 0.4%–3.5% in patients undergoing pulmonary resection for metastasis from any carcinomas and 0.1%–0.26% in patients undergoing gastrectomy for gastric cancer.[15,16] In our study, out of 564 patients who underwent lung metastasectomy, 12 patients (2%) with metastasis from gastric cancer were relatively rare. Because this study was conducted at a single institution and examined very rare cases, the observation period was long.

In the current study, the observation period for the DFI following gastrectomy >12.5 months group was significantly longer than the other group. This may be affected by advances in systematic therapy for gastric cancer; however, there was no difference between the two groups regarding whether or not chemotherapy was administered before pulmonary metastasectomy.

In our department, we underwent pulmonary metastasectomy on selected patients who were considered eligible for surgery based on Thomford's criteria. Because of the lack of data on patients who are ineligible for surgery, we regret that we cannot clarify the validity of our decision-making for surgery.

Conclusion

The DFI following gastrectomy and serum CEA values before pulmonary metastasectomy are associated with prognostic outcomes of patients undergoing surgery for pulmonary metastases from gastric cancer. Eligibility criteria may be established with these factors based on multi-institutional, large-scale study.

Declarations

Ethics approval and consent to participate

This retrospective clinical study was approved by the Kagoshima University Hospital Ethics Committee (Research approval number: 230087). Research participants and their relatives could opt out by viewing the research content hosted online.

Consent for publication

Consent has been obtained from all concerned parties.

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Data availability statement

All data are included in this article. Further inquiries can be directed to the corresponding author.

Author contributions

GK, MA, and KU gave the initial idea. TU and AHT treated the patients. GK, MA, TU, AHT, TN, and KU recollected the data. GK and MA drafted the manuscript. GK and CK performed statistical analysis. All authors read and approved the final manuscript.

Disclosure statement

The authors declare no conflicts of interest associated with this manuscript.

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