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Original Article

Does Preoperative Low HbA1c Predict Esophageal Cancer Outcomes?

Ryosuke Kochi, MD,[1] Takashi Suzuki, MD, PhD,[1] Satoshi Yajima, MD, PhD,[1] Yoko Oshima, MD, PhD,[1] Masaaki Ito, MD, PhD,[2] Kimihiko Funahashi, MD, PhD,[1] and Hideaki Shimada, MD, PhD[1,2]

Background: Although several reports have shown that diabetes is a poor prognostic factor for esophageal cancer, no reports assessed prognostic impact of hemoglobin A1c (HbA1c) in the patients with esophageal cancer. Therefore, we evaluated the prognostic significance of HbA1c in patients with esophageal cancer.
Methods: A total of 137 patients with esophageal carcinoma surgically treated at our institute between 2009 and 2017 were enrolled in this retrospective study. We divided these patients into quarters according to pretreatment levels of HbA1c. We used 5.5% as a cutoff for classifying patients into low (Q1; n = 30) and high (Q2, Q3, Q4; n = 107) HbA1c groups. Univariate and multivariate analyses were then used to evaluate the clinicopathological and prognostic significance of pretreatment level of HbA1c.
Results: There was no significant relationship between HbA1c level and clinicopathological factors. The low HbA1c group had a significantly worse survival rate as compared to that of the high HbA1c group (overall survival $p = 0.04$, relapse-free survival $p = 0.02$). However, the difference was not confirmed in the multivariate analysis.
Conclusion: Although low level of pretreatment HbA1c might be associated with poor prognosis for patients with esophageal cancer, low HbA1c was not an independent risk factor.

Keywords: esophageal cancer, HbA1c, prognosis

Introduction

Diabetes has been reported to increase the risk of various types of cancer, including esophageal cancer.[1,2)] Hemoglobin A1c (HbA1c) measurement has been the widely accepted gold-standard diagnostic of diabetes as it reflects the glucose metabolism over the past 3 months.[3)] Generally, patients with locally advanced esophageal cancer have poor nutritional status due to passage disturbances. Nutritional status is thought to be a prognostic factor for esophageal cancer patients.[4)] In addition, low serum albumin[5)] and high C-reactive protein (CRP)[6)] are reported to be the significant predictors of poor prognosis in such patients. Conflicting reports have proposed a prognostic role of body mass index (BMI) for histologic types of esophageal cancer.[7–9)] Okamura *et al.* reported that a high level of preoperative HbA1c is significantly associated with anastomotic leakage after esophagogastric anastomosis.[10)] Analysis of the impact of preoperative HbA1c revealed that poor glycemic control was an independent risk factor for overall and disease-specific survival following esophagectomy for esophageal squamous cell carcinoma.[11)]

[1]*Department of Surgery, School of Medicine, Toho University, Tokyo, Japan*
[2]*Department of Gastroenterological Surgery & Clinical Oncology, Graduate School of Medicine, Toho University, Tokyo, Japan*

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Corresponding author: Hideaki Shimada, MD, PhD. Department of Gastroenterological Surgery & Clinical Oncology, Graduate School of Medicine, Toho University, 6-11-1 Omori-nishi, Ota-ku, Tokyo 142-8541, Japan
Email: hideaki.shimada@med.toho-u.ac.jp

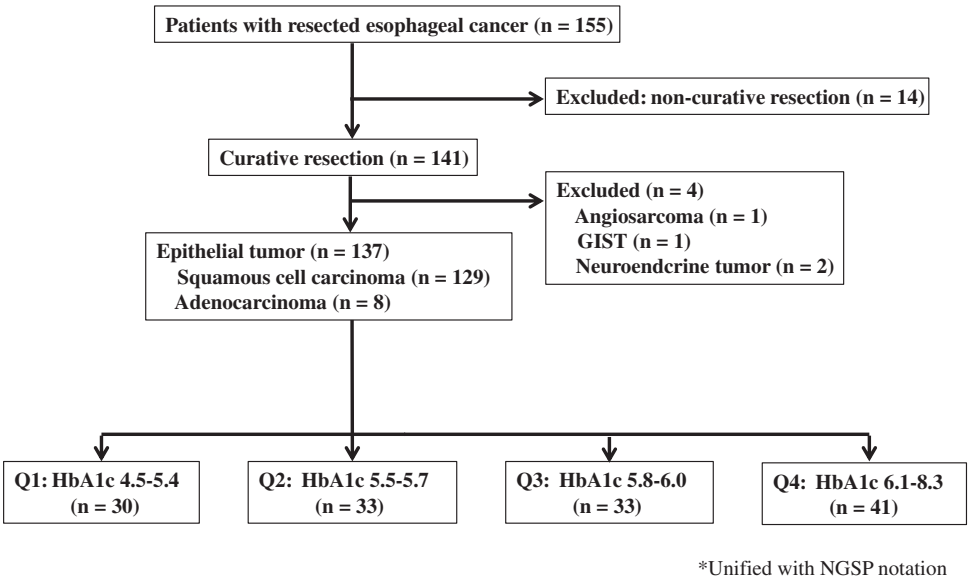

Fig. 1 Flowchart showing patient selection in the present study.

Chronic hyperglycemia induces high levels of HbA1c. Conversely, chronic hypoglycemia may induce low HbA1c levels.[12] Although diabetes has been reported to be a risk factor for early postoperative complications, long-term prognostic impact of diabetes and/or hyperglycemia is still controversial.[13] Moreover, the long-term prognostic impact of HbA1c level has not been evaluated in patients with gastrointestinal cancers. To address this research gap, we evaluated the clinicopathological and prognostic significance of the pretreatment levels of HbA1c in patients with esophageal cancer.

Methods

Patients and definition of high HbA1c

For this retrospective study, 155 patients with esophageal malignant tumors surgically treated at the Omori Medical Center, Toho University School of Medicine (Tokyo, Japan), between October 2009 and February 2017 were identified. Of these, non-curative resection cases (n = 14) and non-epithelial tumors (n = 4, gastrointestinal stromal tumor, angiosarcoma, and neuroendocrine tumors) were excluded (**Fig. 1**). Therefore, we enrolled a total of 137 patients in the present study. Our cohort comprised of 107 males (78%) and 30 females (22%), with a median age of 66 years (range, 39–85 years). Patients were categorized according to tumor stage as follows: stage 0 (n = 10), stage I (n = 27), stage II (n = 39), stage III (n = 49), and stage IV (n = 12). The present study was performed in accordance with the Declaration of Helsinki and approved by the ethics committee of Toho University Hospital (M18002, 21-093, 23-167, 24-001, 26-256).

Information from the patients' medical records was retrospectively reviewed to evaluate the clinical impact of pretreatment level of HbA1c. Also, we used our institutional reference to classify the patients with high CRP levels and low albumin levels. Low BMI was determined based on previous research.[14]

Surgery, adjuvant chemotherapy, and follow-up methods

This retrospective, observational study examined esophageal cancer patients who underwent radical esophagectomy. Lymph nodes were harvested by standard lymphadenectomy (D2) according to the Guidelines for Diagnosis and Treatment of Carcinoma of the Esophagus 2017.[15] In the present study, 71 of 137 patients (52%) underwent neoadjuvant therapy, which consisted of 5-fluorouracil and/or cisplatin.[15]

After surgery, all patients were followed up by clinical examination and imaging on a regular basis until the end of June 2017 or death. The average follow-up for survivors was 44.5 months (range, 0–89 months). In our cohort, 40 patients (29%) survived for more than 3 years. Postoperative cancer recurrence was defined as positive findings on successive monthly clinical examinations, 6-month ultrasonography examination, and annual computed tomography scans.

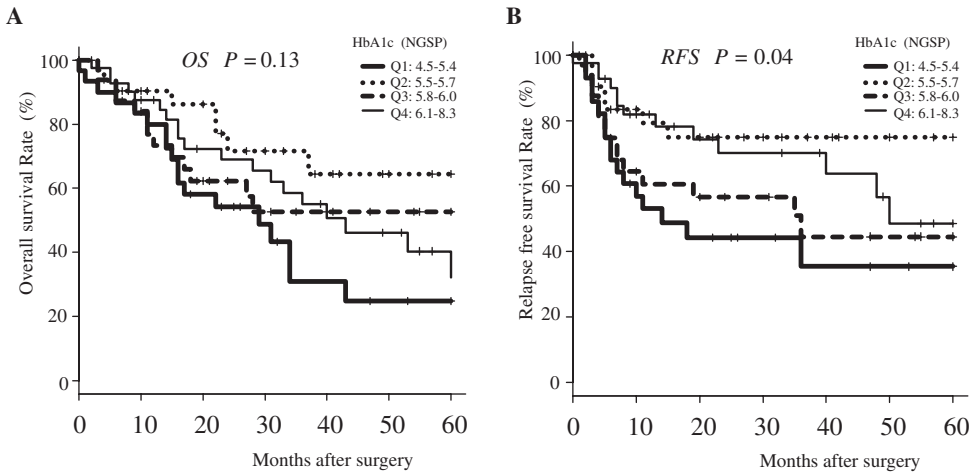

Fig. 2 (**A**) The overall survival ($p = 0.13$; log-rank test) and (**B**) the relapse-free survival ($p = 0.04$; log-rank test) of patients according to quartile analysis of HbA1c levels (Q1:4.5–5.4, Q2:5.5–5.7, Q3: 5.8–6.0, Q4: 6.1–8.3).

Study design and data collection

We examined the patients' clinicopathological factors, including demographics, tumor characteristics, and survival, and subsequently compared these factors between the high and low HbA1c groups. Blood tests, including HbA1c, were performed routinely on venous samples collected before the treatment. Other various serum markers, including blood count, CRP, albumin, and BMI were also evaluated. Univariate and multivariate analyses were used to evaluate the prognostic impact of these variables.

We used a standard flow sheet to collect the data on preoperative parameters, operative variables, pathological parameters, postoperative treatment, and survival to create a dedicated database. The overall survival time for each patient was calculated from the time of surgery. The postoperative survival time and cause of death were recorded for the patients who died, whereas the postoperative survival time and recurrence status were recorded for the survivors.

Statistical analyses

All statistical analyses were performed using EZR statistical software.[16] HbA1c values were expressed as mean ± standard deviation. The clinicopathological and prognostic significance of pretreatment level of HbA1c was evaluated by univariate and multivariate analyses. Comparisons between groups were conducted using Fisher's exact test. Survival curves were calculated using the Kaplan–Meier product limit estimate. Survival differences between groups were analyzed by the log-rank test. Significant predictors identified by univariate analysis were then assessed by multivariate analysis using the Cox proportional hazards model. Two-tailed p values <0.05 were regarded as statistically significant.

Results

Impact of a low HbA1c level on relapse-free survival and overall survival in univariate analysis

We divided the patients into four groups according to HbA1c levels (Q1, Q2, Q3, and Q4, **Fig. 1**). Based on these four levels of HbA1c, overall and relapse-free survival rates were compared in univariate analysis (**Fig. 2**). Among the four groups, Q1 showed the worst survival rates (**Figs. 2A** and **2B**). Therefore, we divided four groups into two groups, Q1 versus Q2, Q3, and Q4 in the following analyses. With the use of a cutoff level for Q1 (HbA1c = 5.5%), we compared the clinicopathological variables in high (n = 107) and low (n = 30) HbA1c groups. The low HbA1c group showed a significantly worse survival rate than high HbA1c group in both overall ($p = 0.04$) and relapse-free survival ($p = 0.02$) (**Figs. 3A** and **3B**).

Comparison of clinicopathological factors between high and low HbA1c groups

Clinicopathological variables were compared in the high HbA1c and low HbA1c groups (**Table 1**). The low HbA1c group was tend to be younger than the high HbA1c group ($p = 0.06$). All patients with high HbA1c group showed normal level of hemoglobin. On the other hand, 59% of low HbA1c group showed low level of hemoglobin (p <0.01). The other clinicopathological variables were not related with HbA1c levels.

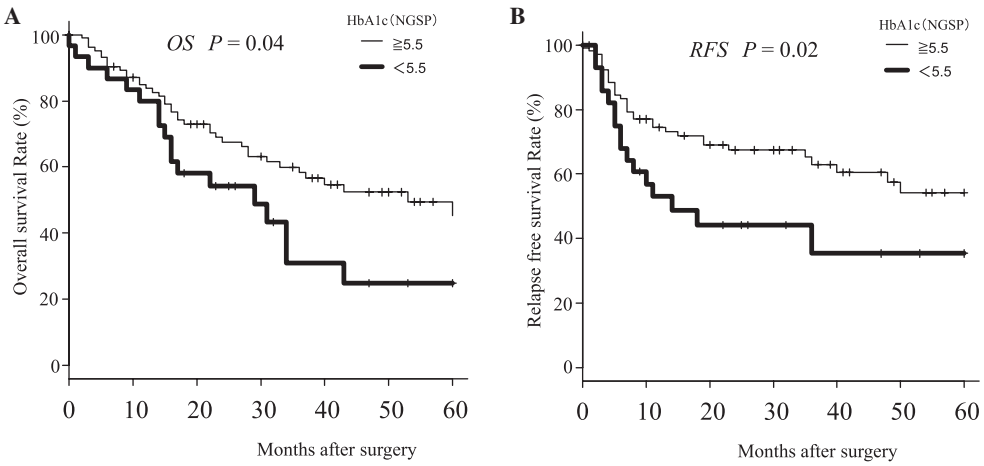

Fig. 3 (**A**) The overall survival ($p = 0.04$; log-rank test) and (**B**) the relapse-free survival ($p = 0.02$; log-rank test) of patients according to HbA1c level <5.5% or ≥5.5.

Table 1 Comparison of pretreatment HbA1c (NGSP) level with clinicopathological factors

Variables		Number of patients (n = 137)	High HbA1c ≥5.5% (n = 107)	Low HbA1c <5.5% (n = 30)	*p* value[a]
Gender	Female	30	24 (80)	6 (20)	1
	Male	107	83 (78)	24 (22)	
Age (year)	<65	56	39 (70)	17 (30)	0.06
	≥65	81	68 (84)	13 (16)	
Tumor depth	T1T2	68	57 (84)	11 (16)	0.15
	T3T4	69	50 (73)	19 (27)	
Nodal status	Negative	60	50 (83)	10 (17)	0.22
	Positive	77	57 (74)	20 (26)	
Stage	0/I/II	76	61 (80)	15 (20)	0.54
	III/IV	61	46 (75)	15 (25)	
Distant metastasis	Negative	133	104 (78)	29 (22)	1
	Positive	4	3 (75)	1 (25)	
WBC count (/l)	<8600	128	100 (78)	28 (22)	1
	≥8600	9	7 (78)	2 (22)	
Hemoglobin (g/dl)	≥11.6	86	86 (100)	0 (0)	<0.01
	<11.6	51	21 (41)	30 (59)	
Platelet count (/l)	$<15.8 \times 10^4$	23	16 (70)	7 (30)	0.28
	$\geq 15.8 \times 10^4$	114	91 (80)	23 (20)	
CRP (mg/dl)	≤0.2	79	63 (80)	16 (20)	0.68
	>0.2	57	43 (75)	14 (25)	
Albumin (g/dl)	≥4.1	48	37 (77)	11 (23)	0.83
	<4.1	89	70 (79)	19 (21)	
BMI	<18.5	28	20 (71)	8 (29)	0.44
	≥18.5	109	87 (80)	22 (20)	

WBC: white blood cell; CRP: c-reactive protein; BMI: body mass index
[a]Fisher's exact probability test

Impact of low HbA1c level on relapse-free survival and overall survival in multivariate analysis

Based on the univariate analysis on survivals, T3T4 tumors (p <0.01), lymph node metastasis (p <0.01), distant metastases (p <0.01), and high CRP ($p = 0.03$) were significant prognostic factors for poor overall survival (**Table 2**). In the multivariate analysis, only lymph node metastasis was an independent prognostic factor (p <0.001). The other factors, including low HbA1c ($p = 0.17$), were not independent prognostic factors for patients with esophageal cancer (**Table 2**).

Table 2 Cox proportional hazards regression analysis and log-rank test analysis for pretreatment high HbA1c (NGSP) group (≥5.5) and clinicopathological factors for overall survival

Variables		Univariate *p* value[a]	Multivariate analysis		
			HR[b]	95% CI[c]	*p* value[d]
Gender	Male Female	0.06	1.58	0.70–3.56	0.27
Tumor depth	T3T4 T1T2	<0.01	1.44	0.74–2.80	0.28
Nodal status	positive negative	<0.01	5.33	2.51–11.31	<0.01
Distant metastasis	positive negative	<0.01	3.09	0.88–10.81	0.08
CRP	≥0.2 <0.2	0.03	0.94	0.53–1.67	0.83
ALB	<4.1 ≥4.1	0.12	1.30	0.69–2.46	0.42
BMI	<18.5 ≥18.5	0.28	1.40	0.71–2.80	0.33
Hemoglobin	< 11.6 ≥ 11.6	0.27	1.56	0.63–3.86	0.34
HbA1c	<5.5 ≥5.5	0.04	1.94	0.76–4.97	0.17

BMI: body mass index; CRP: C-reactive protein; HbA1c: hemoglobin A1c

[a]Log-rank test analysis, [b]Adjusted hazards ratio, [c]Adjusted 95% confidence interval, [d]Cox proportional hazards regression analysis

Recurrences were noted in 51 of the 137 patients (37%). Among the low HbA1c group, 16 of the 30 patients (53%) developed cancer recurrence, including seven lymph node, two local, and seven distant recurrences. By contrast, among the high HbA1c group, 35 of the 107 patients (33%) developed cancer recurrence, including 18 lymph node, 1 local, and 16 distant recurrences. Cancer recurrence patterns did not differ significantly in the two groups.

Discussion

From the evaluation of clinicopathological and prognostic significance of pretreatment level of HbA1c in patients with esophageal cancer, low HbA1c was found to be significantly associated with advanced tumor depth and poor survival.

Although univariate analysis showed that low HbA1c was a poor prognostic factor, it was not an independent factor for survival in the multivariate analysis. The interaction between low HbA1c and advanced tumor stage might be the cause of this discrepancy. Passage disturbance due to advanced tumors could be the main cause of chronic hypoglycemia. At the patient's first clinical visit, HbA1c may be a convenient and useful biomarker for predicting chronic hypoglycemia and advanced tumor stages.

Interestingly, although the difference was not statistically significant ($p = 0.06$), the younger group showed low HbA1c more frequently than the older group. Although younger patients might be more resistant to chronic hypoglycemia, older patients might not be. Another possible explanation for this difference is that elderly patients are more likely to have comorbidities that impair glucose tolerance.

One of the limitation of this study was that we did not assess the impact of glucose tolerance itself. Although low HbA1c is significantly associated with tumor progression, impaired glucose tolerance could impact this association. The other limitations of this study were pseudo-low level due to iron administration and pseudo-high level due to aging and/or iron deficiency anemia. These modifications on HbA1c levels might affected on this study.

In conclusion, low pretreatment level of HbA1c might be associated with tumor depth and poor survival in patients with esophageal cancer. Low pretreatment level of HbA1c may be a convenient marker for predicting malnutrition and advanced tumor stages.

Acknowledgments

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Compliance with Ethical Standards

The present study was performed in accordance with the Declaration of Helsinki and was approved by the ethics committee of Toho University Hospital (M18002, 21-093, 23-167, 24-001, 26-256). We obtained informed consent from all participants.

Disclosure Statement

The authors have no conflict of interest to declare.

References

1) Pan XF, He M, Yu C, et al. Type 2 diabetes and risk of incident cancers in China: a prospective study among 0.5 million Chinese adults. Am J Epidemiol 2018; **187**: 1380–91.
2) Vulcan A, Manjer J, Ohlsson B. High blood glucose levels are associated with higher risk of colon cancer in men: a cohort study. BMC Cancer 2017; **17**: 842.
3) Phillips PJ, Leow S. HbA1c, blood glucose monitoring and insulin therapy. Aust Fam Physician 2014; **43**: 611–5.
4) Wu N, Zhu Y, Kadel D, et al. The prognostic influence of body mass index, resting energy expenditure and fasting blood glucose on postoperative patients with esophageal cancer. BMC Gastroenterol 2016; **16**: 142.
5) Matsuda S, Takeuchi H, Kawakubo H, et al. Prognostic impact of change in the fibrinogen and albumin score during preoperative treatment in esophageal cancer patients. World J Surg 2017; **41**: 2788–95.
6) Zheng TL, Cao K, Liang C, et al. Prognostic value of C-reactive protein in esophageal cancer: a meta-analysis. Asian Pac J Cancer Prev 2014; **15**: 8075–81.
7) Pan W, Sun Z, Xiang Y, et al. The correlation between high body mass index and survival in patients with esophageal cancer after curative esophagectomy: evidence from retrospective studies. Asia Pac J Clin Nutr 2015; **24**: 480–8.
8) Miao L, Chen H, Xiang J, et al. A high body mass index in esophageal cancer patients is not associated with adverse outcomes following esophagectomy. J Cancer Res Clin Oncol 2015; **141**: 941–50.
9) Wong JY, Shridhar R, Almhanna K, et al. The impact of body mass index on esophageal cancer. Cancer Control 2013; **20**: 138–43.
10) Okamura A, Watanabe M, Imamura Y, et al. Preoperative glycosylated hemoglobin levels predict anastomotic leak after esophagectomy with cervical esophagogastric anastomosis. World J Surg 2017; **41**: 200–7.
11) Okamura A, Watanabe M, Imamura Y, et al. Glycemic status and prognosis of patients with squamous cell carcinoma of the esophagus. World J Surg 2017; **41**: 2591–7.
12) Torimoto K, Okada Y, Tanaka Y, et al. Usefulness of hemoglobin A1c and glycated albumin measurements for insulinoma screening: an observational case-control study. BMC Cancer 2019; **19**: 174.
13) Yao W, Meng Y, Lu M, et al. Impact of type 2 diabetes mellitus on short-term and long-term outcomes of patients with esophageal squamous cell cancer undergoing resection: a propensity score analysis. Cancer Commun (Lond) 2018; **38**: 14.
14) Tomita M, Ayabe T, Nakamura K. Low body mass index is an independent predictive factor after surgical resection in patients with non-small cell lung cancer. Asian Pac J Cancer Prev 2017; **18**: 3353–6.
15) The Japan Esophageal Society. Guidelines for Diagnosis and Treatment of Carcinoma of the Esophagus 2017. Tokyo: Kanehara Co, 2017.
16) Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant 2013; **48**: 452–8.