



Impact of metformin on survival outcome of esophageal squamous cell carcinomas patients undergoing surgical resection: a multicenter retrospective study

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Background: Diabetes mellitus is a recognized risk factor for esophageal squamous cell carcinomas (ESCC), and metformin is a recognized protective factor for some gastrointestinal tumors. But knowledge is limited regarding the effect of metformin on survival outcome of ESCC patients with type 2 diabetes mellitus (T2DM). We assessed the impact of post-diagnosis metformin use on overall survival (OS) and disease-free survival (DFS) in ESCC with T2DM undergoing surgical resection.

Methods: A retrospective analysis was performed on 3,523 patients with ESCC who met the study conditions after surgical resection. Log-rank and Cox regression models were used to evaluate the relationship between metformin and T2DM and ESCC survival rate, and adjusted according to age, gender, BMI, smoking, drinking and staging, *et al.*

Results: Among included ESCC patients, 619 were associated with type 2 diabetes, while the remaining 2,904 were not associated with type 2 diabetes. The 5-year OS (28.43%) of patients with T2DM was significantly lower than that of patients without T2DM (32.75%), $P=0.037$. DFS in 5 years were 27.30% (with T2DM) and 31.75% (without T2DM) ($P=0.030$), respectively. Compared with patients without T2DM, patients with T2DM presented worse OS [adjusted risk ratio (HR_{adj}) = 1.19] and DFS (HR_{adj} = 1.17; $P < 0.001$). Among the 619 patients with type 2 diabetes, 485 were treated with metformin and 134 were not treated with metformin. Patients treated with metformin had significantly improved OS [adjusted risk ratio (HR_{adj}) = 0.89; $P=0.031$] and DFS (HR_{adj} = 0.90; $P=0.013$).

Conclusions: T2DM was again associated with poorer survival in ESCC patients, and metformin may improve the prognosis of these patients.

Keywords: Esophageal squamous cell carcinomas (ESCC); type 2 diabetes mellitus (T2DM); metformin; overall survival (OS); disease-free survival (DFS)

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Introduction

For malignant tumors, diabetes is not only one of the causes of morbidity, but also one of the risk factors leading to poor survival (1-4). The effect of diabetes on the survival of esophageal cancer is currently controversial. The effect of diabetes on the survival of patients with esophageal cancer has been studied by many scholars. Most studies confirm that diabetes mellitus is associated with a worse survival (4), however, some studies suggest that diabetes is not an independent risk factor for survival (5,6).

The treatment of type 2 diabetes mellitus (T2DM), especially metformin, has been proved by numerous studies in recent years to improve the survival of patients with malignant tumors (7-10). For patients with esophageal squamous cell carcinoma (ESCC), many molecular mechanisms have been proved that metformin can inhibit tumor progression (11-13). However, the inhibitory effect of metformin on ESCC lacks direct follow-up observation with big data. Another point to ponder is whether metformin has a consistent tumor-suppressing effect in all patients with ESCC.

In this study, we first used a large sample to re-examine the effect of type 2 diabetes on ESCC survival outcomes. Since metformin is believed to improve the survival of some cancer patients, we conducted subgroup analysis to further investigate whether the relationship between T2DM and ESCC outcome is related to metformin.

Methods

Patients

The institutional review board of five hospitals involved in this study approved this study. All subjects involved in the study provided informed consent. Briefly, we collected patients with newly diagnosed ESCC pathologically from 2008 to 2013. All patients underwent surgical resection. Basic information (including age, sex, smoking status, alcohol consumption, BMI) was collected by consulting inpatient medical records. Phone or email to collect follow-up data. The follow-up data were completed with the assistance of the household registration department and hospitals. The data collection route is shown in *Figure 1*.

Main observation indicators

The most important outcome measure is overall survival (OS), defined as from the date of surgery to the date of death or the

last known survival date. The second major outcome measure was disease-free survival (DFS), defined as the time between the date of surgery and the recurrence of cancer.

Statistical analysis method

Data were compared across subgroups using OS and DFS. Informed consent Associations between T2DM and outcomes were estimated using the method of Kaplan-Meier to generate survival curves and assessed using the log-rank tests. Cox proportional hazards models were used as primary analyses, adjusting for age, gender, stage, performance status, smoking status and drinking status, and BMI. The same method was used to evaluate the associations between metformin use and outcomes for patients ESCC with T2DM. Factorial design was used to evaluate whether two factors interact. All reported P values are from two-sided tests. P value less than 0.05 was considered statistically significant. All statistical analyses used SPSS software version 20.0.

Results

Basic information of patients

Finally, 3,523 ESCC patients were included in this study, and 2,432 patients relapsed and 2,396 died within 5 years after surgery. The mean follow-up time for these patients was 39.2 months (1.9–72.0 months). The 5-year OS and DFS of those patients included in this study were 31.99% and 30.97%, respectively. Gender, smoking status and drinking status were significantly different between ESCC with T2DM and without T2DM. For ESCC with T2DM patients, divided into two subgroups by the absence versus presence of metformin use. Gender, smoking status, drinking status, and TNM stage were no significantly different between these two subgroups. General information and clinical treatment of all patients were shown in *Table 1*.

Relationship between T2DM and OS and DFS

First, Kaplan-Meier curves were drawn, and the results showed that T2DM was significantly correlated with OS deterioration (log-rank test, $P < 0.001$; *Figure 2A*). The 5-year OS rates of patients with T2DM was significantly lower than that of patients without T2DM (28.43% vs. 32.75%, log-rank test, $P < 0.001$).

Univariate analysis showed that with T2DM was

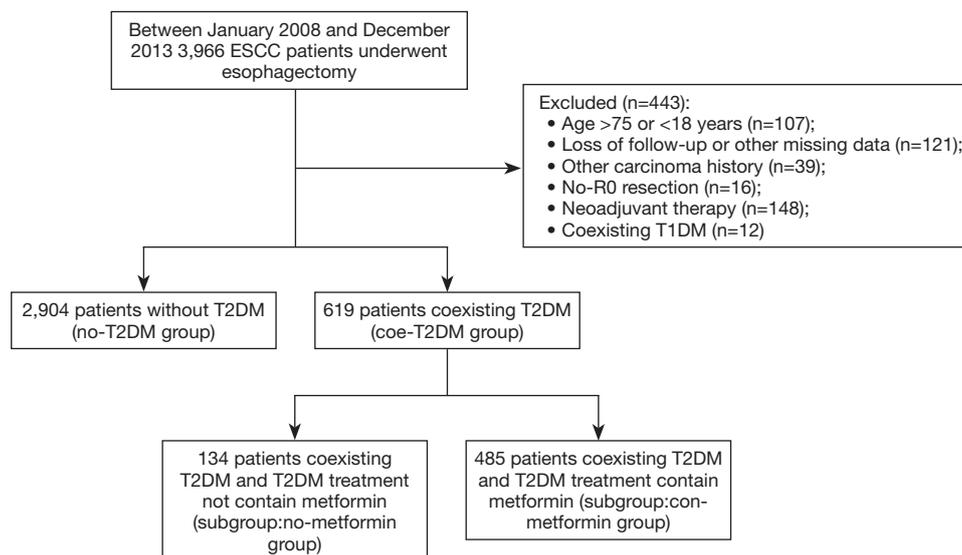


Figure 1 Flow chart of patient screening in this study. T2DM, type 2 diabetes mellitus.

associated with worse OS after surgery for ESCC patients (HR =1.24; 95% CI, 1.12–1.38; $P<0.001$). In the multivariate Cox proportional hazard model adjusting for gender, smoking status and drinking status, the adjusted hazard ratio (HR adj) for T2DM was 1.19 (95% CI, 1.10–1.29; $P<0.001$) when compared with non-T2DM (Table 2).

The same statistical method was used to analyze the effect of T2DM on DFS, and the results was similar to the results of OS, and that T2DM was significantly correlated with DFS deterioration (log-rank test, $P<0.001$; Figure 2B) ($P<0.001$). The 5-year DFS rates in patients with T2DM was significantly lower than those without T2DM (27.30% vs. 31.75%, log-rank test, $P=0.03$). Univariate analysis shown that T2DM was significantly associated with worse DFS (HR =1.23; 95% CI, 1.11–1.37; $P<0.001$). After a similar multivariate adjustment, HR adj for T2DM was 1.17 (95% CI, 1.08–1.26; $P<0.001$) when compared with non-T2DM (Table 3).

Relationship between metformin and OS and DFS for ESCC with T2DM patients

In stratified analyses, Kaplan-Meier curves showed that metformin use were significantly associated with better OS (Log-rank test, $P=0.014$; Figure 2C) and DFS (Log-rank test, $P=0.015$; Figure 2D). The 5-year OS rates in patients with metformin use (30.72%) was significantly higher than that without metformin use (20.15%) ($P=0.014$), and the 5-year DFS rates in patients with metformin use (29.48%) was significantly higher than those without metformin use (19.40%) ($P=0.015$).

In the univariate analysis, metformin use was significantly associated with better OS (HR =0.76; 95% CI, 0.61–0.95; $P=0.015$) and DFS (HR =0.76; 95% CI, 0.62–0.95; $P=0.015$). In the multivariate Cox proportional hazard model adjusting for clinical variables, HR_{adj} for metformin use was 0.89 (95% CI, 0.80–0.99; $P=0.031$) for OS and 0.90 (95% CI, 0.83–0.98; $P=0.013$) for DFS relative to the absence of metformin use (Tables 4, 5).

We further compared 5-year survival of group no-T2DM and subgroup coe-metformin, univariate COX regression indicated that there was difference in survival between the two groups (OS: HR =0.85; 95% CI, 0.75–0.95, $P=0.004$; DFS: HR =0.86; 95% CI, 0.77–0.97, $P=0.010$), and K-M curve showed that the survival benefit brought by metformin could not offset the survival harm brought by T2DM (Figure 3).

Discussion

Because of the complex pathogenesis and early symptoms are atypical of ESCC, most patients are in the progressive stage at the time of diagnosis (14). Although the treatment has been improving, including surgery and comprehensive treatment, the prognosis is still very unsatisfactory (15).

In recent years, many studies have found that the drugs used for some chronic diseases may affect the prognosis of tumors (16). Diabetes is considered to be one of the causes of esophageal cancer (5). Meanwhile, as one of the conventional drugs for diabetes treatment, metformin has been proved to improve the prognosis of patients by

Table 1 Demographic and clinical characteristics for patients with ESCC

Characteristics	No-T2DM (n=2,904)	coe-T2DM (n=619)		P value ^{&}
		Con-metformin (n=485)	No-metformin (n=134)	
Gender				
Male	73.31% [2,129]	47.63% [231]	38.81% [52]	<0.001
Female	26.69% [775]	52.37% [254]	61.19% [82]	
Age, years	63.14±8.22	59.94±9.41	60.44±7.23	<0.001
Smoking history	48.79% [1,417]	41.65% [202]	35.07% [47]	<0.001
Alcohol history	45.66% [1,326]	42.68% [207]	37.31% [50]	<0.001
Distance between tumour to incisor teeth, cm	26.23±5.19	27.03±6.11	26.19±5.04	0.102
Tumour location				0.502
Cervix segment	10.02% [291]	8.04% [39]	9.70% [13]	
Upper thoracic segment	18.46% [536]	20.21% [98]	23.88% [32]	
Middle thoracic segment	49.10% [1,426]	44.95% [218]	48.51% [65]	
Lower thoracic segment	22.42% [651]	26.80% [130]	17.91% [24]	
Stage of TNM				0.704
IA	8.06% [234]	7.63% [37]	6.72% [9]	
IB	10.09% [293]	11.96% [58]	9.70% [13]	
IIA	19.59% [569]	18.35% [89]	17.91% [24]	
IIB	26.55% [771]	27.01% [131]	35.07% [47]	
IIIA	19.04% [553]	18.76% [91]	15.67% [21]	
IIIB	12.29% [357]	13.20% [64]	10.45% [14]	
IVA	4.37% [127]	3.09% [15]	4.48% [6]	
Preoperative BMI; Kg/m ²	21.27±4.03	22.17±7.23	20.89±4.11	0.059
Preoperative glycosylated hemoglobin; %	–	6.43±2.07	6.81±2.99	0.094 [#]
Postoperative glycosylated hemoglobin; %	–	5.45±1.98	5.79±2.47	0.099 [#]
Anastomotic fistula	0.59% [17]	1.24% [6]	3.73% [5]	0.003
Postoperative chemotherapy	80.13% [2,327]	78.56% [381]	79.10% [106]	0.412
Postoperative radiotherapy	78.82% [2,289]	75.46% [366]	78.36% [105]	0.134
Outcome				
Tumor related death	66.49% [1,931]	69.07% [335]	77.61% [104]	0.03
Death	67.25% [1,953]	69.28% [336]	79.85% [107]	0.037
Relapse/progression	68.25% [1,982]	70.52% [342]	80.60% [108]	0.03
Mean survival time, month	40.9	39.2	30.1	
Mean DFS, month	36.2	32.5	27.1	
5-year OS	32.75% [951]	30.72% [149]	20.15% [27]	0.037*
5-year DFS	31.75% [922]	29.48% [143]	19.40% [26]	0.03*

[&], it indicates the difference between group no-T2DM (n=2,904) and group coe-T2DM (n=619); [#], it indicates the difference between group con-metformin (n=485) and group no-metformin (n=134); *, P value of the chi-square test, $P_{\log\text{-rank}}=0.014, 0.015$, separately for OS and DFS. ESCC, esophageal squamous cell carcinomas; T2DM, type 2 diabetes mellitus; OS, overall survival; DFS, disease-free survival.

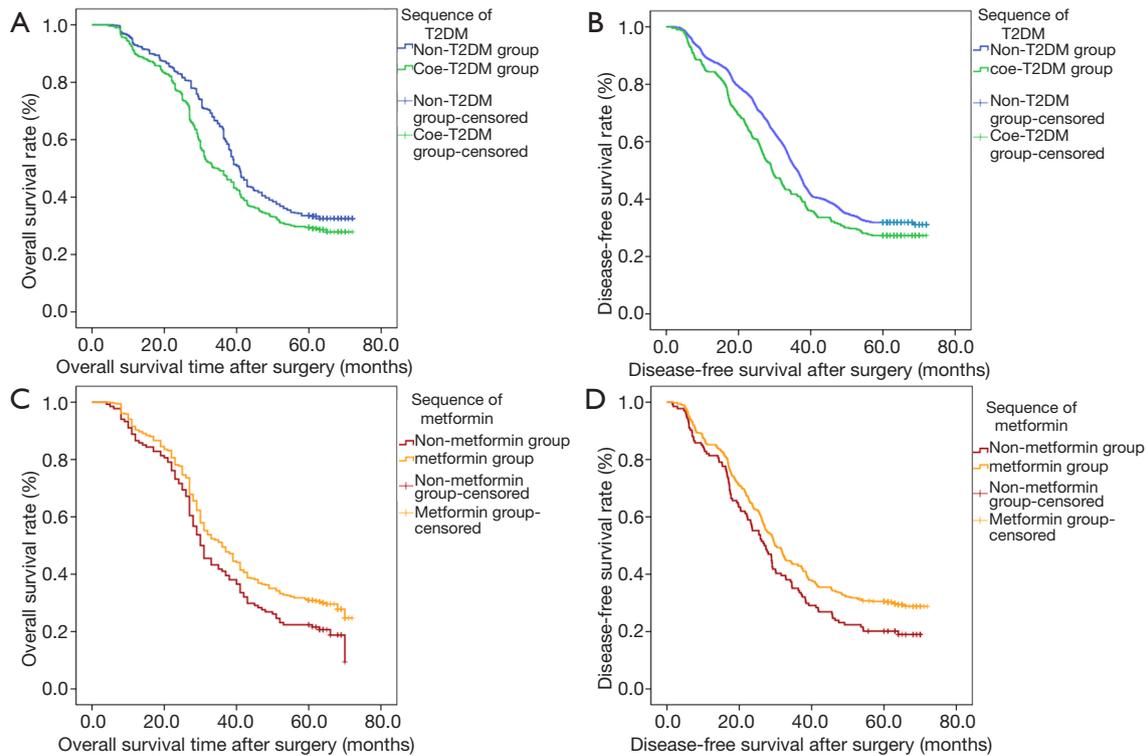


Figure 2 (A) Kaplan-Meier estimates of overall survival by overall cohort; non-T2DM group: 2,904 patients, T2DM group: 619 patients, $P_{\text{Log-Rank}} < 0.001$; (B) Kaplan-Meier estimates of DFS by overall cohort; non-T2DM group: 2,904 patients, T2DM group: 619 patients, $P_{\text{Log-Rank}} < 0.001$; (C) Kaplan-Meier estimates of overall survival by subgroup cohort; metformin group: 485 patients, non-metformin group: 134 patients, $P_{\text{Log-Rank}} = 0.014$; (D) Kaplan-Meier estimates of DFS by subgroup cohort; metformin group: 485 patients, non-metformin group: 134 patients, $P_{\text{Log-Rank}} = 0.015$. T2DM, type 2 diabetes mellitus; DFS, disease-free survival.

Table 2 Hazard ratios (HRs) for overall survival (OS) according to clinic variables among ESCC patients

Variables	Univariate		Multivariate	
	HR (95% CI)	P value	HR _{adj} (95% CI)	P value
Age (years)	1.17 (1.06–1.29)	0.002	1.18 (1.07–1.31)	0.001
Gender				
Male	Reference		Reference	
Female	0.85 (0.61–1.18)	0.34	0.88 (0.65–1.20)	0.421
Smoking history	1.09 (1.02–1.17)	0.014	1.03 (0.98–1.08)	0.235
Alcohol history	1.07 (0.91–1.26)	0.423	1.09 (0.92–1.30)	0.334
BMI at diagnosis	0.64 (0.46–0.89)	0.008	0.71 (0.55–0.93)	0.011
Anastomotic fistula	1.17 (0.68–2.02)	0.584	1.12 (0.63–1.99)	0.712
Stage of TNM	1.96 (1.22–3.15)	0.005	1.78 (1.13–2.81)	0.013
T2DM				
Non-T2DM	Reference		Reference	
Coe-T2DM	1.24 (1.12–1.38)	<0.001	1.19 (1.10–1.29)	<0.001

*, adjusted for all variables shown in table. ESCC, esophageal squamous cell carcinomas; T2DM, type 2 diabetes mellitus.

Table 3 Hazard ratios (HRs) for disease-free survival (DFS) according to clinic variables among ESCC patients

Variables	Univariate		Multivariate	
	HR (95% CI)	P value	HR _{adj} (95% CI)	P value
Age (years)	1.16 (1.05–1.29)	0.005	1.17 (1.05–1.30)	0.004
Gender				
Male	Reference		Reference	
Female	0.82 (0.57–1.16)	0.277	0.87 (0.63–1.19)	0.398
Smoking history	1.11 (1.00–1.23)	0.048	1.06 (0.94–1.20)	0.355
Alcohol history	1.06 (0.99–1.13)	0.084	1.08 (0.91–1.28)	0.383
BMI at diagnosis	0.61 (0.48–0.83)	<0.001	0.70 (0.58–0.85)	<0.001
Anastomotic fistula	1.17 (0.68–2.02)	0.584	1.12 (0.63–2.00)	0.714
Stage of TNM	1.91 (1.19–3.07)	0.007	1.83 (1.15–2.91)	0.011
T2DM				
Non-T2DM	Reference		Reference	
Coe-T2DM	1.23 (1.11–1.37)	<0.001	1.17 (1.08–1.26)	<0.001

*, adjusted for all variables shown in table. ESCC, esophageal squamous cell carcinomas; T2DM, type 2 diabetes mellitus.

Table 4 Hazard ratios (HRs) for overall survival (OS) according to clinic variables among ESCC patients with T2DM

Variables	Univariate		Multivariate	
	HR (95% CI)	P value	HR _{adj} (95% CI)	P value
Age (years)	1.04 (0.91–1.19)	0.578	1.10 (1.03–1.18)	0.006
Gender				
Male	Reference		Reference	
Female	0.91 (0.82–1.01)	0.076	0.82 (0.68–0.99)	0.038
BMI at diagnosis	0.69 (0.53–0.89)	0.005	0.78 (0.65–0.96)	0.012
Preoperative glycosylated hemoglobin; %	1.04 (0.96–1.13)	0.351	1.05 (0.97–1.13)	0.212
Postoperative glycosylated hemoglobin; %	1.13 (1.07–1.20)	<0.001	1.07 (1.02–1.13)	0.009
Anastomotic fistula	1.09 (0.62–1.91)	0.777	1.02 (0.56–1.85)	0.953
Stage of TNM	2.23 (1.54–3.23)	<0.001	2.16 (1.42–3.29)	<0.001
Metformin				
No-metformin	Reference		Reference	
Con-metformin	0.76 (0.61–0.95)	0.015	0.89 (0.80–0.99)	0.031

*, adjusted for all variables shown in table. ESCC, esophageal squamous cell carcinomas; T2DM, type 2 diabetes mellitus.

improving the pathological remission rate of neoadjuvant therapy for esophageal cancer (17).

Metformin is one of the most widely prescribed glucose-lowering agents for treatment of type 2 diabetes mellitus (T2DM) due to its superior safety profile and few side

effects such as lactic acidosis and hypoglycemia (18). It has the dual effect of reducing the body weight and blood glucose of obese patients (19), making it one of the preferred drugs for obese T2DM patients. However, both obesity and diabetes are risk factors for tumorigenesis

Table 5 Hazard ratios (HRs) for disease-free survival (DFS) according to clinic variables among ESCC patients with T2DM

Variables	Univariate		Multivariate	
	HR (95% CI)	P value	HR _{adj} (95% CI)	P value
Age (years)	1.05 (0.97–1.14)	0.239	1.10 (1.03–1.17)	0.003
Gender				
Male	Reference		Reference	
Female	0.93 (0.85–1.02)	0.119	0.80 (0.65–0.98)	0.033
BMI at diagnosis	0.71 (0.55–0.91)	0.008	0.77 (0.61–0.96)	0.024
Preoperative glycosylated hemoglobin; %	1.09 (0.91–1.31)	0.36	1.13 (0.98–1.30)	0.089
Postoperative glycosylated hemoglobin; %	1.21 (1.10–1.33)	<0.001	1.16 (1.06–1.27)	0.001
Anastomotic fistula	1.05 (0.78–1.41)	0.759	1.03 (0.75–1.40)	0.863
Stage of TNM	2.08 (1.67–2.59)	<0.001	1.97 (1.58–2.46)	<0.001
Metformin				
No-metformin	Reference		Reference	
Con-metformin	0.76 (0.62–0.95)	0.015	0.90 (0.83–0.98)	0.013

*, adjusted for all variables shown in table. ESCC, esophageal squamous cell carcinomas; T2DM, type 2 diabetes mellitus.

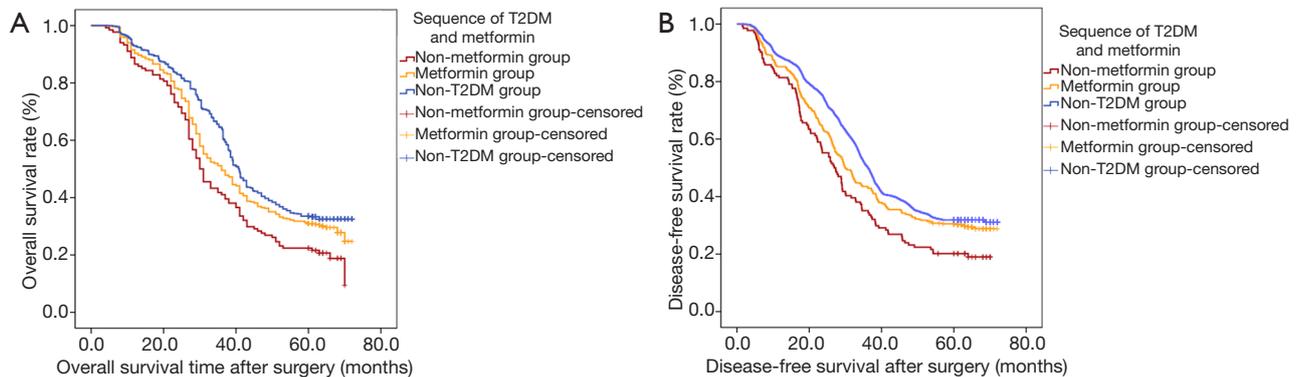


Figure 3 (A) Kaplan-Meier estimates of overall survival by overall cohort; non-T2DM group: 2,904 patients, metformin group: 485 patients, non-metformin group: 134 patients, $P_{\text{Log-Rank}} < 0.001$; (F) Kaplan-Meier estimates of disease-free survival by overall cohort; non-T2DM group: 2,904 patients, metformin group: 485 patients, non-metformin group: 134 patients, $P_{\text{Log-Rank}} < 0.001$. T2DM, type 2 diabetes mellitus.

(1,5,20,21), does metformin reduce tumor incidence by reducing the patient's weight or by controlling the patient's diabetes? It has not been confirmed. Previous studies have elucidated this mechanism from a molecular biological perspective (10,13), but there is a lack of large sample multicentric clinical observations.

In previous clinical studies, the effect of metformin on the prognosis of esophageal cancer is controversial. Some studies have shown that metformin does not improve the prognosis of patients with esophageal cancer and may

even weaken the efficacy of chemotherapy drugs (22,23). However, Sekino (12) prompt that metformin showed antitumor effects by inhibiting cell proliferation, tumor growth and Epithelial-mesenchymal transition (EMT) and inducing apoptosis in ESCC cell lines and xenograft models. These effects may have been induced by inhibiting NF- κ B activation on ESCC. In addition to, Damelin *et al.* (23,24) show that the copper-bis (thiosemicarbazones), Cu-ATSM and Cu-GTSM, which are trapped in cells under reducing conditions, cause significant ESCC cytotoxicity,

both alone and in combination with metformin.

The continuous development of molecular biology research provides impetus and theoretical support for us to carry out this multi-center and large-sample retrospective study.

Based on these previous studies, our study first confirmed that T2DM is indeed an independent risk factor for the prognosis of patients with ESCC through large sample data, and the combination of T2DM will indeed bring a worse prognosis, which is consistent with previous studies (1,5,25). In the stratified analysis, metformin was found to provide significant survival benefits for ESCC with T2DM patients. Of course, by looking at the K-M curve, we also found that metformin improved the prognosis of patients with T2DM with ESCC, this improvement did not seem to offset the risk of T2DM itself (Figure 3A,B).

Limitations

As a retrospective study, this paper has insuperable limitations. First, we missed the data of postoperative BMI changes of ESCC patients. The BMI mentioned in this study is patient's BMI at the time of diagnosis. Most patients with esophageal cancer will lose weight after surgery (26), and metformin will also reduce the weight of diabetic patients, which will directly affect the recurrence of tumor. Therefore, the relationship between ESCC, metformin and weight change are worth further study. Secondly, fasting and postprandial blood glucose monitoring are the direct methods to compare blood glucose control in patients with diabetes. However, such data are missing in our study. HbA1C can only reflect the overall control of blood glucose in recent months, and cannot accurately reflect the fluctuation of blood glucose. Does metformin bring better prognosis to patients because of better blood glucose control in patients with esophageal cancer after surgery (1)? Thirdly, how does the endocrinologist decide whether to use metformin in the treatment of diabetes, and will these conditions affect the prognosis of patients? Fourthly, the anticancer effect of metformin may be related to the synergistic effect of other drugs, which has been confirmed by other studies (23,27,28). However, our retrospective study lacks the use record of other drugs when taking metformin. Finally, the biggest doubt for ours, whether ESCC without T2DM patients can benefit from metformin? Our team is applying to the ethics committee to conduct a multi-center, large-sample, prospective, randomized clinical study to address the above questions.

Conclusions

Coexisting T2DM is associated with worse survival outcomes in ESCC patients, and metformin may improve the prognosis of these patients.

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Footnote

Conflicts of Interest: JH serves as the unpaid Executive Editor-in-Chief of *Journal of Thoracic Disease*. The other authors have no conflicts of interest to declare

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by the ethics committee of the first affiliated hospital of Guangzhou medical university, and ethics committee of all participating institutions agree to implement.

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