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Original Article

Factors pertaining to long-term mortality following emergency visits for head and neck cancer

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KEYWORDS
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Abstract *Background/purpose:* Avoiding mortality has been the ultimate goal in the management of head and neck cancer (HNC) patients with emergency department (ED) visits, however, risk factors and causes of mortality are not well studied. The objective of the present study is to verify the factors associated with long-term mortality of patients with HNC who visited ED.
Materials and methods: We retrospectively collected data of 1660 HNC patients who made ED visits from the Longitudinal Health Insurance Database 2000 during 2000–2012 in Taiwan. The multivariate Cox proportional hazard model was used to measure the mortality-associated risk factors in HNC patients who made ED visits.
Results: The prognostic factors associated with mortality risk were age (≥65 vs. < 65 y; HR = 1.58, p < 0.0001), geographic region (central vs. northern; HR = 1.20, p = 0.0384; southern vs. northern; HR = 1.38, p = 0.0001), surgery (yes vs. no; HR = 0.61, p < 0.0001), radiotherapy (yes vs. no; HR = 1.80, p < 0.0001), chemotherapy (yes vs. no; HR = 1.68, p < 0.0001), acute myocardial infarction (yes vs. no; HR = 2.01, p = 0.0303), diabetes mellitus (yes vs. no; HR = 1.60, p < 0.0001), chronic obstructive pulmonary (yes vs. no; HR = 1.51,

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p = 0.0002), number of ED visits (≥4 vs. 1; HR = 0.69, p = 0.0003), and number of admissions (1 vs. 0; HR = 1.54, p < 0.0001; ≥2 vs. 0; HR = 1.48, p = 0.0002).
Conclusion: Higher mortality was associated with older age, living in southern Taiwan, not having undergone surgery, having received radiotherapy and chemotherapy, comorbidities, and more hospital admissions. A coordinated and extended multidisciplinary approach including ED care is required to improve the long-term survival and further decrease the economic burden of HNC treatment.

Introduction

Head and neck cancer (HNC) includes malignant tumors that occur in the oral cavity, paranasal sinuses, nasal cavity, pharynx, and larynx.[1] HNC is the sixth most common cancer, accounting for approximately 6% of all cancer cases.[2,3] It has been estimated that in Taiwan alone, there were 7248 newly oral cavity, oropharynx and hypopharynx cancer patients diagnosed, representing about 7.31% of all cancers in 2013.[4]

There are two aspects to cancer patients' visiting the emergency department (ED). One aspect may be considered suitable care while we assess and manage acute onset problems, but the other may be unable to adequately manage during routine outpatient or inpatient treatment.[5] Nevertheless, new treatment strategies for cancer patients has resulted in prolonged life-spans and increased numbers of visits to EDs by cancer patients.

Few studies have investigated the factors associated with mortality following visits to EDs by cancer patients. Previous studies had reported 48% of advanced non-small-cell lung carcinoma (NSCLC) patients had visited the ED within the 30 days preceding their deaths.[6] Lung cancer patients who were admitted to the intensive care unit (ICU) survived were 32% and 11% of those who received mechanical ventilation were still alive after 6 months.[7] Additionally, long-term survival was lower and costs of care were higher for patients who were hospital readmitted.[8] In general, hospital readmissions are costly, lead to fragmentation of care, poorer prognoses, and reduce the window of opportunity for recommended adjuvant therapy types.[9,10] These results can instruct us on how to reduce hospital admissions resulting from poor prognoses.

In our previous literature,[11] we found that survival rate of HNC patients significantly decreased over time in the ED visitor group compared with the non-ED visitor group. In addition, HNC patients had higher rates of ED visits and admissions than other cancer patients, particularly, the May, June, and July were three top-ranked months for ED visits. Moreover, evaluating survival time and verifying factors related to mortality after HNC patients' ED visits is important and could lead to better patient prognoses through the induction of appropriate interventions. Therefore, the present study is further to investigate risk factors associated with long-term mortality of patients with HNC who visited ED by using the nationwide population-based data set of the Taiwan National Health Insurance Research Database (NHIRD).

Materials and methods

Data sources

We used the Longitudinal Health Insurance Database 2000 (LHID2000), which is a subset of the National Health Insurance Research Database (NHIRD) and comprises registration files and medical claims data for 1,000,000 patients are randomly sampled from all enrollees. Beginning in 1995, Taiwan had established NHI program and covered approximately 99% of the entire population. Prior studies demonstrated the validity of the claims data in the NHI database.[12,13]

All information are confidential that encrypts patients' personal information to protect privacy and provides researchers with anonymous identification numbers in accordance with the data regulations of the National Health Insurance Bureau (NHIB) and the Taiwan National Health Research Institute (NHRI). This study was approved by the Institutional Review Board of Kaohsiung Veterans General Hospital (VGHKS15-EM4-01).

Study population

The HNC patient subpopulation was identified using the Catastrophic Illness Patient Database. To select the retrospective cohort study, we identified 1660 patients aged 20 years or older at time of HNC (ICD-9-CM codes 140–149) diagnosis who made ED visits between January 1, 2000, and December 31, 2012.

Identification of sample

The index date for each patients was newly diagnosed with HNC date. Study were observed until death, withdraw of the database or the end of December 31, 2012.

The research collected categorical sociodemographic factors, including gender, age group (<65 years and ≥65 years), hospital characteristics (medical center hospitals; others: regional or district hospitals), geographic region (northern, central, southern, or eastern Taiwan)diagnostic site of the HNC (oral cavity: unspecified parts of mouth, tongue, gum, lip, floor of mouth; non-oral cavity: oropharynx, hypopharynx, unspecified parts of pharynx), number of ED visits (1, 2–3, ≥4 times) and number of admissions (0, 1, ≥2 times).

Definitions of the rapies, patients received the therapy (surgery or radiotherapy or and chemotherapy) between diagnosed with HNC date and ED-visit date. Comorbidity (Acute myocardial infarction, AMI; Diabetes mellitus, DM; Hypertension; chronic obstructive pulmonary disease, COPD) were defined as the presence codes before diagnosed with HNC date.

The survival time, age group, gender, hospital characteristics, geographic region, diagnostic site of the HNC, surgery, radiotherapy, chemotherapy, AMI, DM,

Table 1 Demographic characteristics of HNC patients who presented to an ED (n = 1660) and 3-, 5-, and 10-year survival rates.

	n (%)	3-year		5-year		10-year	
		Survival rate (%)	p-value[a]	Survival rate (%)	p-value[a]	Survival rate (%)	p-value[a]
Gender			0.6914		0.1416		0.121
Male	1521 (91.63)	56.92		48.05		38.20	
Female	139 (8.37)	59.05		58.97		48.38	
Age group			<0.0001		<0.0001		<0.0001
< 65 years	1293 (77.89)	60.72		52.98		41.65	
≥ 65 years	367 (22.11)	44.40		34.84		29.85	
Hospital characteristics			0.0026		0.0033		0.0059
Medical center	1183 (71.27)	59.57		51.27		40.61	
Others	477 (28.73)	50.60		42.62		35.08	
Geographic region			0.0265		0.0203		0.0443
Northern	632 (38.07)	62.12		53.78		42.79	
Central	436 (26.27)	56.26		48.36		35.66	
Southern	543 (32.71)	52.83		44.92		37.81	
Eastern	49 (2.95)	48.57		36.95		31.67	
Site			<0.0001		<0.0001		<0.0001
Oral cavity	497 (29.94)	62.72		55.07		46.70	
Non-oral cavity	1163 (70.06)	58.74		50.81		40.96	
Surgery			<0.0001		<0.0001		<0.0001
No	756 (45.54)	44.89		38.67		33.33	
Yes	904 (54.46)	67.20		57.50		43.42	
Radiotherapy			<0.0001		<0.0001		<0.0001
No	599 (36.08)	71.96		67.15		59.68	
Yes	1061 (63.92)	48.95		39.07		28.02	
Chemotherapy			<0.0001		<0.0001		<0.0001
No	863 (51.99)	67.64		60.63		53.24	
Yes	797 (48.01)	45.70		36.29		23.69	
Acute myocardial infarction	0.00		0.0284		0.0099	0.00	0.0119
No	1646 (99.16)	57.32		49.18		39.15	
Yes	14 (0.84)	33.02		24.76		24.76	
Diabetes mellitus			<0.0001		<0.0001		<0.0001
No	1478 (89.04)	58.51		50.48		40.30	
Yes	182 (10.96)	45.59		36.39		28.61	
Hypertension			0.0006		<0.0001		0.0002
No	1371 (82.59)	58.71		51.12		40.48	
Yes	289 (17.41)	49.23		37.75		32.46	
COPD			<0.0001		<0.0001		<0.0001
No	1484 (89.40)	58.86		51.08		40.55	
Yes	176 (10.60)	42.05		30.12		25.82	
Number of ED visits			0.0135		0.0284		0.2167
1	517 (31.14)	57.93		52.07		47.07	
2—3	532 (32.05)	53.38		44.82		38.48	
>4	611 (36.81)	60.02		50.64		35.42	
Number of admissions			<0.0001		<0.0001		<0.0001
0	798 (48.07)	65.22		57.86		50.06	
1	489 (29.46)	47.80		40.39		32.74	
>2	373 (22.47)	52.72		42.62		28.46	

HNC: Head and neck cancer; ED: emergency department; COPD: chronic obstructive pulmonary disease.
[a] Log-rank p-value.

hypertension, COPD, number of ED visits and number of admissions were obtained for statistical analysis.

Statistical analysis

We compared the cumulative incidences of outcomes among various groups by the modified Kaplan—Meier method and log-rank test. The association between factors and risk of mortality in HNC patients was estimated by multivariate Cox proportional hazards model. SAS®9.4 (SAS Institute Inc., Cary, NC, USA) was used for the data analyses.

Results

Patient characteristics

Demographic characteristics of HNC patients are detailed in Table 1. Over a period of 12 years (2000—2012), 1660 patients with HNC visited the ED. Among the patients, 91.63% were males, 8.37% were females, and 22.11% were 65 years of age and older. The majority of the HNC patients visited EDs at medical centers (n = 1,183, 71.27%) rather than at others (regional or district hospitals) (n = 477, 28.73%). In addition, more patients visited EDs in the densely populated cities in Taiwan (northern, central and southern) than those in sparsely populated areas (eastern: n = 49, 2.95%). Most patients, 1163 (70.06%), were non-oral cavity. Nearly half, 904 (54.46%), of patients underwent surgery; 1061 (63.92%) patients received radiotherapy; and 797 (48.01%) received chemotherapy. For comorbidities, 14 (0.84%) had AMI, 182 (10.96%) had DM, 289 (17.40%) had HTN, and 176 (10.60%) had COPD.

Regarding the number of ED visits, 517 (31.14%) patients had visited the ED one time, 532 (32.04%) patients had visited 2 to 3 times, and 611 (36.80%) patients had visited more than 3 times. 798 (40.87%) patients did not require admission to the hospital, 489 (29.46%) patients were admitted one time and 373 (22.47%) patients were admitted more than once.

Regarding the prognoses of the HNC patients who had visited an ED, through 2012, 866 (52.17%) patients had died; the remaining patients were still alive. The 3-, 5-, and 10-year survival rates after diagnosis were 57.11%, 48.97%, and 39.05%, respectively. The mean interval from discharge to ED visit of the patients was 1.36 ± 1.89 years (not shown in tables).

Table 1 shows that lower survival rates at 3, 5, and 10 years in HNC patients who made ED visits were associated with older age, non-medical hospital and non-oral cavity. In terms of therapies, the 3-, 5-, 10-year, and overall survival were higher in patients who had undergone surgery, but lower in patients who received radiotherapy and chemotherapy (Table 1, Fig. 1). In addition, lower survival in HNC patients was associated with comorbidity, including AMI, DM, HTN and COPD (Table 1, Fig. 2).

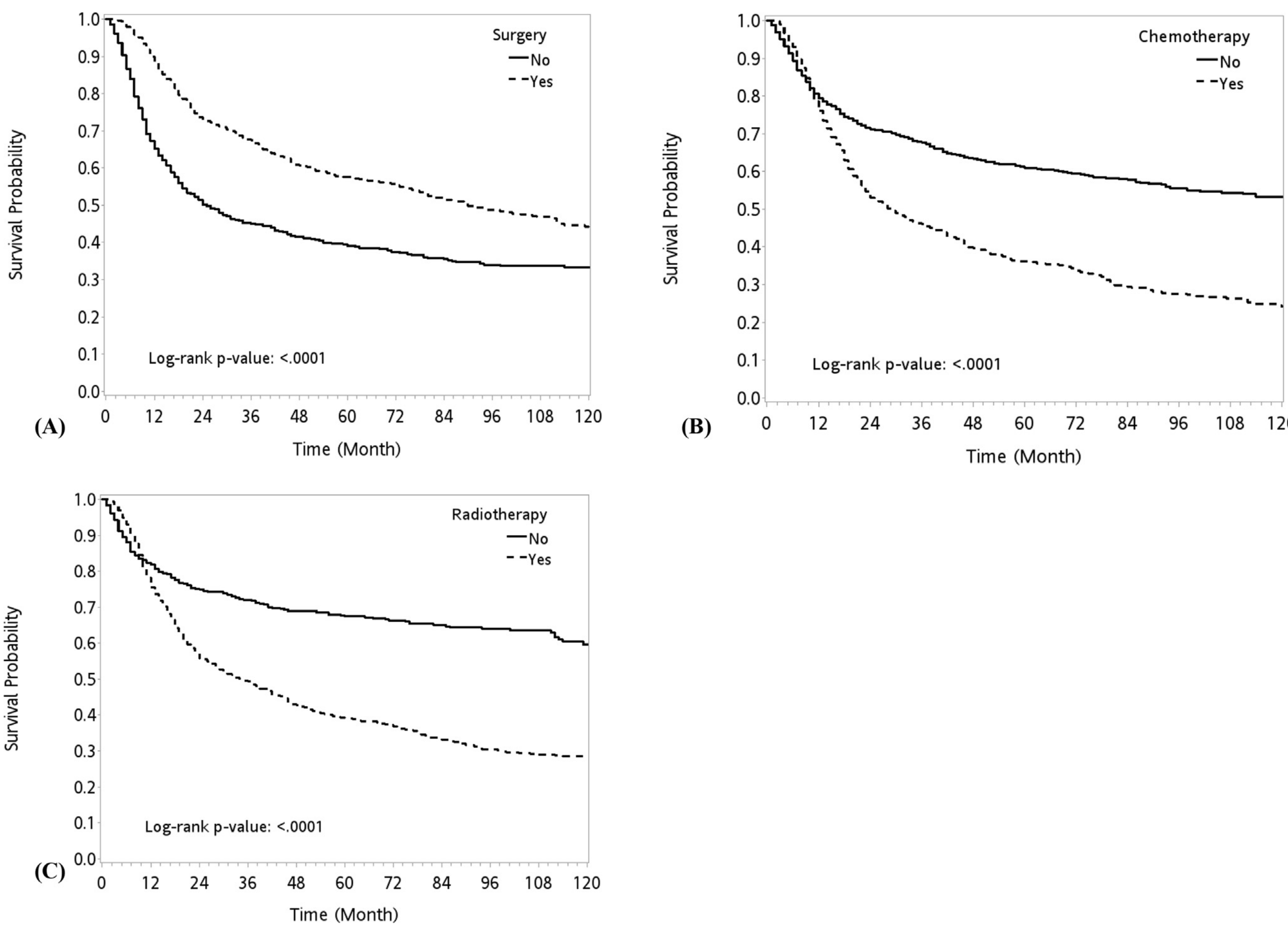

Fig. 1 Kaplan—Meier curves of overall survival for therapy types: (A) Surgery, (B) Chemotherapy and (C) Radiotherapy.

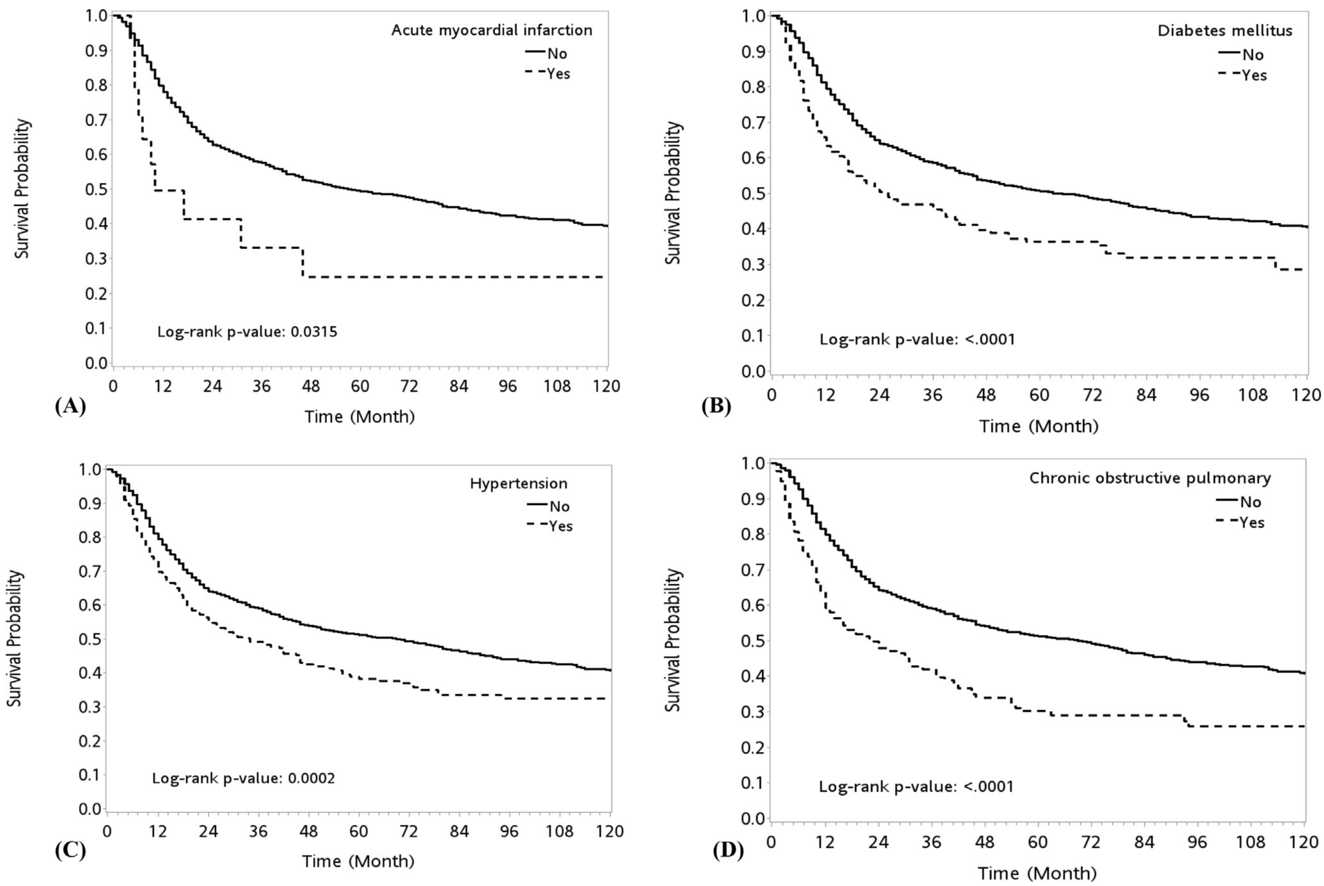

Fig. 2 Kaplan—Meier curves of overall survival for comorbidities: (A) Acute myocardial infarction, (B) Diabetes mellitus, (C) Hypertension, and (D) Chronic obstructive pulmonary.

Moreover, number of ED visits and admissions were associated with survival.

Adjusted risk factors for mortality in HNC patients with ED visits

Table 2 shows the results of univariate and multivariate Cox proportional hazards analyses for risk factors associated with mortality in HNC patients who made ED visits. After multivariate analysis, age group, geographic region, surgery, radiotherapy, chemotherapy, AMI, DM, COPD, number of ED visits and number of admissions were independent risk factors associated with mortality. Older age ($\geq$65 years) (HR = 1.58, 95% CI = 1.34—1.85, $p < 0.0001$) and residing in central (HR = 1.20, 95% CI = 1.01—1.43, p = 0.0384) or southern (HR = 1.38, 95% CI = 1.17—1.63, p = 0.0001) were positively associated with mortality. For therapy types, patients with surgery had a significantly lower risk of mortality than patients without surgery (HR = 0.61, 95% CI = 0.53—0.70, $p < 0.0001$). However, patients with radiotherapy (HR = 1.80, 95% CI = 1.49—2.17, $p < 0.0001$) or chemotherapy (HR = 1.68, 95% CI = 1.43—1.99, $p < 0.0001$) had a higher risk of mortality. In terms of comorbidities, AMI (HR = 2.01, 95% CI = 1.07—3.78, p = 0.0303), DM (HR = 1.60, 95% CI = 1.29—2.00, $p < 0.0001$) and COPD (HR = 1.51, 95% CI = 1.21—1.87, p = 0.0002) were independent unfavorable factors among HNC patients who visited ED. Notably, patients with more than four ED visits (vs. one visit, HR = 0.69, 95% CI = 0.57—0.85, $p < 0.0001$) had lower risk of mortality.

Discussion

This study explored the factors associated with long-term mortality of patients with HNC who visited ED. By adopting nationwide population-based claim data, a sufficient number of patients with HNC who made ED visits (n = 1660) were retrieved for analysis. To our knowledge, this is currently the largest patient enrollment for this condition. We identified factors of age, geographic, surgery, radiotherapy, chemotherapy, comorbidities (AMI, DM and COPD), and hospital admissions associated with mortality.

The majority of elderly HNC patients had locally advanced tumors at the time of initial presentation.[14] Numerous studies have shown that compared with younger patients, older HNC patients are less liable to receive potentially curative treatment,[15—17] and only half of the older HNC patients comply with their institutions' therapeutic strategies.[1,18] In our study, which focused on HNC patients who made ED visits, older patients tended toward lower survival rates. In contrast, a number of studies suggest that the survival outcomes for older and younger HNC patients are similar.[1,19]

Table 2 Cox proportional hazard model for risk factors associated with mortality among HNC patients who made ED visits.

	Univariate HR	95%CI	*p-value*	Multivariate HR	95%CI	*p-value*
Gender						
Male vs. Female	1.22	0.95–1.58	0.1233	1.00	0.76–1.29	0.9381
Age group						
≥65 years vs. age <65 years	1.57	1.35–1.83	<0.0001	1.58	1.34–1.85	<0.0001
Hospital characteristics						
Others vs. Medical center	1.22	1.06–1.42	0.0069	1.05	0.90–1.22	0.5241
Geographic region						
Central vs. Northern	1.16	0.98–1.37	0.0927	1.20	1.01–1.43	0.0384
Southern vs. Northern	1.23	1.05–1.45	0.0105	1.38	1.17–1.63	0.0001
Eastern vs. Northern	1.44	0.99–2.11	0.0594	1.21	0.82–1.78	0.3494
Site						
Non-oral cavity vs. Oral cavity	1.44	1.25–1.66	<0.0001	0.94	0.80–1.09	0.4095
Surgery						
Yes vs. No	0.57	0.50–0.65	<0.0001	0.61	0.53–0.70	<0.0001
Radiotherapy						
Yes vs. No	2.22	1.90–2.61	<0.0001	1.80	1.49–2.17	<0.0001
Chemotherapy						
Yes vs. No	1.97	1.72–2.26	<0.0001	1.68	1.43–1.99	<0.0001
Acute myocardial infarction						
Yes vs. No	1.96	1.05–3.65	0.0347	2.01	1.07–3.78	0.0303
Diabetes mellitus						
Yes vs. No	1.56	1.28–1.91	<0.0001	1.60	1.29–2.00	<0.0001
Hypertension						
Yes vs. No	1.38	1.16–1.63	0.0002	1.08	0.89–1.31	0.4673
COPD						
Yes vs. No	1.77	1.45–2.16	<0.0001	1.51	1.21–1.87	0.0002
Number of ED visits						
2–3 vs. 1	1.13	0.95–1.34	0.1677	0.93	0.77–1.11	0.3942
≥4 vs. 1	1.02	0.86–1.20	0.8418	0.69	0.57–0.85	0.0003
Number of admissions						
1 vs. 0	1.71	1.46–2.00	<0.0001	1.54	1.31–1.81	<0.0001
≥2 vs. 0	1.56	1.32–1.84	<0.0001	1.48	1.21–1.82	0.0002

HNC: Head and neck cancer; ED: emergency department; COPD: chronic obstructive pulmonary; HR, hazard ratio.

In our study, the 3-, 5- and 10-year survival rates for patients who visited medical centers were 57.11%, 48.97% and 39.05%, respectively, and the patients who visited regional and district hospitals had lower rates (50.60%, 42.62%–35.08%). Mulvey et al. found that after head and neck surgeries, high-volume hospital care related to decreased risk of death and failure to rescue compared with low-volume care, that appears to be associated with differences in responses to and management of complications.[20] However, no significant association was present between hospital teaching level and mortality, and this finding appears to be comparable with previous literature.[21]

We found that there was a favorable correlation among HNC patients who had undergone surgery, but having received radiotherapy and/or chemotherapy was a contrary independent factor for poor survival. Surgery and radiotherapy have long been the cornerstone treatment modalities for HNC patients, especially in the early stages.[22] The concurrent use of chemotherapy during radiotherapy is now an important option as the definitive[23] or adjuvant treatment for locally advanced HNC.[24] However, each of these interventions has side effects and might cause unanticipated morbidities.[25,26] It is not difficult to imagine that patients with HNC who underwent surgeries had better survival, and this can be explained by their having been in the early, operable stages of their cancers. However, no detailed information was available regarding the patients' cancer stages or therapy regimens and whether the individuals had been under clinical care for their cancers when they visited the ED.

Among HNC populations, comorbidity tends to increase with age,[27] and other factors such as race, gender and socioeconomic issues are also related to increased incidence and severity of comorbidity. Coatesworth et al. suggested that 40% of deaths in HNC patients were secondary to comorbid conditions.[28] In a study of HNC patients who were treated with concurrent chemoradiotherapy, deaths caused by comorbidities occurred at a median of 1.9 years.[1] Hall et al. showed that 16% more deaths were caused by comorbidity in the first 3 years after treatment.[29] In our study, risk of mortality in HNC patients was associated with comorbid diseases, including AMI, DM and COPD, and our results were comparable with those from previous studies.

However, Paleri et al. demonstrated that comorbidity increases mortality in HNC patients and that this effect is better in the early years following treatment and in younger patients.[30] In the present study, comorbidity (AMI, DM and COPD) and older age were simultaneously independent factors for mortality in HNC patients who visited ED. The opposite effect of aging may reflect differing etiologies (e.g., human papillomavirus, alcohol and tobacco use history) and the increasing incidence of oropharyngeal cancer in younger populations.[31]

It has been shown that type 2 DM is a risk factor for a number of malignancies.[32] The risk of HNC in patients with DM has rarely been found, and inconsistent results have been reported for this relationship.[33] Campbell et al. found that diabetic men had a significant risk of oral cavity cancer mortality.[34] In the present study, the HNC patients with DM had poor survival, therefore, further researches of the underlying mechanisms is needed, but that was out of compass of our study.

In the present study, we used COPD as a surrogate for smoking. Maasland et al. found that cigarette smokers had an incidence rate of 4.49 for HNC, 2.11 for oral cavity cancer, 8.53 for oropharyngeal and hypopharyngeal cancer, and 8.07 for laryngeal cancer.[35] A number of studies also concurred that cigarette smoking had a higher risk of the larynx or pharynx than of the oral cavity. It might be the aerodynamics of respiratory flow in the upper airway, which could expose the larynx and pharynx to more inhaled air than the oral cavity receives. It appears reasonable that non-oral cavity cancers would have lower survival rates than oral cavity cancers.[36,37]

Regarding hospitalization, 40.87% of patients did not require hospital admission, although 59.13% of patients were admitted. HNC patients appeared to have more ED visits and admissions than other cancer types.[5] The differences of ED visits and admission rates for the wide-ranging reasons could not be fully interpretation based on our administrative database, and additional patient-level factors, such as disease stages and therapy regimen.

A previous study found that 48% NSCLC patients had visited the ED within the 30 days preceding their deaths.[6] In our study, 17.4% of patients had died less than 1 month after their ED visits. Notably, patients with more than four ED visits (vs. one) had better survival rates but not those with two or three ED visits. The time-dependent effects appear to demonstrate that risk factors may vary over time, resulting in weaker or stronger associations.[38]

Slatore et al. found that 32% lung cancer were admitted to ICU survived, but only 11% of whom with mechanical ventilation were still alive after 6 months.[7] In addition, worse long-term survival and higher costs of care in patients who were readmitted.[8] Moreover, hospital readmissions are costly, lead to fragmentation of care and poorer prognoses, and obstruct the golden time for recommended adjuvant therapies.[9,10] Our study showed that number of admissions was an independent factor for poor survival. These results were comparable with those of previous studies and tell us how we can reduce admissions based on poor prognoses.

In our study, the NHIRD for the period between 2000 and 2012 provided a systematic and consistent method for capturing data on a large number of HNC patients who made ED visits ($n = 1660$). There is force in the large sample size in our study, which increased the statistical power and the exactitude of the risk estimation in our analyses. However, there were a number of limitations for NHIRD database: first, it's a secondary database, thus it was collected for clinical and administrative purposes; second, some visits that were cancer-related may have been missed or not have been included; third, it was difficult to confirm cancer-specific mortality based on the registry data; fourth, administrative databases don't comprise fully information such as patients' cancer stages, laboratory values, vital signs and treatment complication (such as speech, swallowing, taste, and smell), in addition, it cannot be indicated whether the individuals were under clinical care for their cancers when they visited the ED; fifth, the findings derived from cohort studies are lower methodological quality than from randomized trials because cohort studies are subject to certain biases related to adjusting for confounders.

This study is the first to use a population-based evaluation that the factors were associate with risk of mortality in patients with HNC who visited ED. Higher mortality was associated with older age, living in southern (vs. northern) Taiwan, not having undergone surgery, having received radiotherapy and chemotherapy, comorbidities (AMI, DM and COPD), and more hospital admissions. Although this study provides valuable information, we must learn more about these patients before and after these visits. With such knowledge, we may be able to estimate ED use as a potential quality indicator of healthcare and formulate policies for how to decrease consumption of ED.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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