Risk factors for rebleeding and long-term outcomes in patients with head and neck cancer bleeding: a multicenter study

Chih-Kai Wang1, Che-Fang Ho2, Kuang-Yu Niu3, Chia-Chien Wu4, Yun-Chen Chang5, Chien-Han Hsiao6 and Chieh-Ching Yen1,7*

Abstract
Background: Acute, catastrophic bleeding in patients with head and neck cancer (HNC) is challenging and also a burden for their families and frontline physicians. This study analyzed the risk factors for rebleeding and long-term outcomes in these patients with HNC.

Methods: Patients who presented to the emergency department (ED) with HNC bleeding were enrolled in this study (N = 231). Variables of patients with or without rebleeding were compared, and associated factors were investigated using Cox’s proportional hazard model.

Results: Of the 231 patients enrolled, 112 (48.5%) experienced a recurrent bleeding event. The cumulative rebleeding incidence rate was 23% at 30 days, 49% at 180 days, and 56% at 1 year. Multivariate Cox regression analyses demonstrated that overweight-to-obesity (HR = 0.52, 95% CI 0.28–0.98, p = 0.043), laryngeal cancer (hazard ratio [HR] = 2.13, 95% confidence interval [CI] 1.07–4.23, p = 0.031), chemoradiation (HR = 1.49, 95% CI 1.001–2.94, p = 0.049), and second primary cancer (HR = 1.75, 95% CI 1.13–2.70, p = 0.012) are significant independent predictors of rebleeding, and the prognostic factors for overall survival included underweight (HR = 1.89, 95% CI 1.22–2.93, p = 0.004), heart rate > 110 beats/min (HR = 1.58, 95% CI 1.04–2.39, p = 0.032), chemoradiation (HR = 2.31, 95% CI 1.18–4.52, p = 0.015), and local recurrence (HR = 1.74, 95% CI 1.14–2.67, p = 0.011).

Conclusions: Overweight-to-obesity is a protective factor, while laryngeal cancer, chemoradiation and a second primary cancer are risk factors for rebleeding in patients with HNC. Our results may assist physicians in risk stratification of patients with HNC bleeding.

Keywords: Rebleeding, Head and neck cancer, Risk factor, Outcome

Introduction
Head and neck cancer (HNC) refers to a heterogeneous disease that includes cancers involving the oral cavity, pharynx, and larynx. On average, patients with HNC have a 5-year survival rate of ~60% [1]. However, they usually emerge at a late stage, with a 5-year survival rate of less than 25% for stage IV squamous cell carcinoma despite aggressive treatment [2]. Traditionally, alcohol drinking and tobacco smoking are the most important risk factors for HNC. Different from Western countries, the unique habit of betel nut chewing with or without tobacco is popular in Taiwan, which is also a well-established risk factor for HNC [3]. These patients tend to have tumor recurrence and poor prognosis compared with those who do not chew betel nut [3]. Betel nut...
chewing has been implicated in precipitating increased risk of HNC bleeding [4].

Acute bleeding from the head and neck area is one of the most life-threatening complications that may occur in patients with HNC. Several predisposing factors have been reported to contribute to HNC bleeding, the main factors being surgery (e.g., radical neck dissection), chemoradiation, wound infection, poor nutritional status, presence of a pharyngocutaneous fistula, tumor recurrence, and a higher T stage [5]. Historically, deconstructive therapy in the form of surgical ligation has been the most widely used treatment. Emergent surgical intervention can result in a neurological complication rate of 60% and an overall mortality rate of 40% [2]. In recent years, radiological intervention, such as deconstruction using endovascular embolization or reconstruction with covered stents, has become the frontline treatment for HNC bleeding if angiography shows contrast media extravasation, pseudoaneurysm, and irregular artery contours [1, 2, 6].

Despite improved treatment modalities, the outcomes in patients with HNC bleeding remain dismal due to acute clinical severity and advanced cancer stage [4, 7, 8]. HNC bleeding is a significant source of psychological burden for patients and their families, and acute, catastrophic bleeding can be challenging for frontline physicians [9, 10]. Prior studies have evaluated clinical outcomes in patients with HNC bleeding [4, 7, 8, 11–15]. However, until now, no studies have analyzed risk factors for patients who are at increased risk of rebleeding. This study aimed to examine the risk factors for rebleeding and the predictors of long-term overall survival in patients with index HNC bleeding.

Materials and methods
Study design and setting
This was a retrospective, multicenter, observational study using regularly collected electronic medical records (EMRs). The study site was the emergency department (ED) of five hospitals using the same EMR system in Taiwan, including two tertiary medical centers and three regional hospitals. The study site’s total capacity was more than 9000 beds and an annual ED visit by 500,000 patients. The study was performed in accordance with the Declaration of Helsinki and with the approval of the Chang Gung Medical Foundation institutional review board (IRB no. 202102021B0).

All adult patients with HNC who met the inclusion criteria from January 1, 2015, to December 31, 2016, were eligible for enrollment. Patients were followed-up regularly until the date of death or the date on which they were last evaluated. The last follow-up date of all patients was September 30, 2021.

Patient selection and data collection
First, we used EMRs to identify all adult patients with the International Classification of Diseases Tenth Revision (ICD-10) codes of HNC (C00-C14 and C30-C32) who were treated in the ED during the study period. Second, we determined eligible patients using the following keywords: bleeding, hemorrhage, and carotid blowout. Patients with inadequate EMRs, duplicate ED visit data, and bleeding events originating from other sites, such as gastrointestinal bleeding, intracranial hemorrhage, and vaginal bleeding, were excluded. Two patients with nasal bleeding were excluded after being examined by otolaryngologists as the bleeding was deemed unrelated to HNC. The patients selected by EMRs were reviewed by two physicians (authors Chih-Kai Wang and Chieh-Ching Yen).

Clinical data, such as age, sex, body mass index (BMI), hypertension, diabetes mellitus, lifestyle factors, vital signs, white blood cell count, hemoglobin, platelet count, international normalized ratio, creatinine, alanine aminotransferase, and imaging modalities, were collected at the time of the first HNC bleeding in the ED. Information about HNC included the primary cancer site, the tumor–node–metastasis (TNM) stage according to the American Joint Committee on Cancer 7th edition, the pathologic type, cancer treatment modality, local recurrence, and a second primary cancer.

If treatment with local compression and packing failed in patients with active, life-threatening HNC bleeding, computed tomography (CT) angiography was performed. The underlying bleeding mechanism was tumor-related cause, pseudoaneurysm, postoperative complication, or fistula formation. Tumor-related causes included contrast extravasation, hypervascular tumor staining, or great vessel involvement on CT angiography or bleeding from a necrotic wound of the tumor confirmed by otolaryngologists with or without fiberoptic endoscopy. Pseudoaneurysm and fistula formation were confirmed by CT angiography.

Treatment methods for patients with HNC bleeding, that is, supportive care, endovascular therapy, or surgical intervention, were determined by a multidisciplinary team comprising otolaryngologists, oncologists, interventional radiologists, and emergency physicians. Supportive care consisted of medication with oral or intravenous tranexamic acid, epinephrine-soaked gauze packing, or observation. Endovascular therapy consisted of transarterial embolization and covered stent graft placement for bleeding involving the common carotid artery, internal carotid artery, or external carotid artery.
including its branches. Surgical intervention consisted of surgical ligation and primary repair. Data of patients who required blood transfusion were also recorded. The primary outcome was a rebleeding event, and the secondary outcome was overall survival. Rebleeding was defined as the recurrence of bleeding after index HNC bleeding recorded in each EMR.

**Statistical analysis**

Clinical data, presentations of cancer, bleeding characteristics, and treatment modality are shown as numbers (percentages) for categorical variables and the mean ± standard deviation (SD) for continuous variables. Comparisons between patients with or without a rebleeding event were made using a chi-square test or Fisher’s exact test, where appropriate, for categorical variables and independent Student’s t-tests or Mann–Whitney U-tests for continuous variables, depending on the distribution characteristics of the variables.

To determine independent risk factors for rebleeding and overall survival, all relevant variables that showed a significant association on univariate analysis were further analyzed using the multivariate Cox proportional hazards model. Cumulative survival curves were generated using Kaplan–Meier curve analysis and compared using the log-rank test.

All statistical analyses were performed using SPSS Statistics version 26 (SPSS Inc., Chicago, IL, USA), and a two-sided p-value of < 0.05 was considered statistically significant.

**Results**

**Patient characteristics**

A total of 231 patients with HNC met the inclusion criteria and were included in the study (Fig. 1). Table 1 summarizes the clinical characteristics of patients stratified by the rebleeding status. The mean age was 56.7 ± 10.9 years, and the BMI was 21.5 ± 3.95 kg/m², with 215 (93.1%) patients being men. Of the 231 patients, 135 (58.4%) were hospitalized, 90 (39%) were discharged from the ED, and 6 (2.6%) died in the ED. In addition, 30 (13%) patients died during hospitalization. The most common cancer sites for patients with HNC bleeding were the oral cavity (n = 94, 40.7%), followed by the nasopharynx (n = 45, 19.5%), hypopharynx (n = 42, 18.2%), oropharynx (n = 34, 14.7%), and larynx (n = 16, 6.9%). More than half the patients were at an advanced HNC stage, and almost all patients had pathologically confirmed squamous cell carcinoma (n = 230, 99.6%). In addition, 92 (39.8%) patients had local recurrence, while 63 (27.3%) had a second primary cancer.

With regard to initial cancer treatment, 117 of 231 (50.6%) patients underwent surgical resection; of them, 100 (43.3%) underwent concomitant neck dissection and 80 (34.6%) concurrent flap reconstruction. Additionally, 179 of 231 (77.5%) patients underwent primary or adjuvant concurrent chemoradiotherapy, whereas 20 (8.7%) patients had no cancer-associated treatment, given either perceived concerns regarding treatment side effects or not-yet-arranged therapy at the time of diagnosis.

Comparison between patients with or without rebleeding showed that compared with the nonrebleeding group, the rebleeding group had a significantly higher proportion of smoking history (85.7% vs. 74.8%; p = 0.038) and a nonsignificantly higher proportion of second primary cancer (33% vs. 21.8%; p = 0.056).

When patients were stratified by second primary cancer, patients with second primary cancer had a significantly more frequent rate of chemoradiation compared...
BMI 21.5

Smoking history 185(80.1) 96(85.7) 89(74.8) 0.038*

Diastolic blood pressure (mmHg) 84.9

Heart rate (beats/min) 102.6

Systolic blood pressure (mmHg) 139.7

Male 215(93.1) 106(94.6) 109(91.6) 0.362

Laboratory exam

Diabetes mellitus 51(22.1) 20(17.9) 31(26.1) 0.133

Hypertension 84(36.4) 38(33.9) 46(38.7) 0.455

Variable Total N = 231 Rebleeding N = 112 Non-rebleeding N = 119 P value

Age (year) 56.7 ± 10.9 55.4 ± 100 580.0 ± 11.5 0.073

Male 215(93.1) 106(94.6) 109(91.6) 0.362

BMI 21.5 ± 3.9 21.4 ± 3.9 21.6 ± 4.0 0.743

Systolic blood pressure (mmHg) 139.7 ± 35.5 140.3 ± 34.0 139.2 ± 37.0 0.807

Diastolic blood pressure (mmHg) 84.9 ± 18.2 85.5 ± 18.3 84.4 ± 18.2 0.643

Heart rate (beats/min) 102.6 ± 22.5 102.4 ± 22.2 102.8 ± 22.9 0.893

Smoking history 185(80.1) 96(85.7) 89(74.8) 0.038*

Betel nut chewer 157(68.0) 77(68.8) 80(67.2) 0.804

Hypertension 84(36.4) 38(33.9) 46(38.7) 0.455

Diabetes mellitus 51(22.1) 20(17.9) 31(26.1) 0.133

Laboratory exam

WBC (10³/µl) 11.5 ± 8.2 12.1 ± 10.1 11.0 ± 6.0 0.297

Hb (g/dl) 10.8 ± 2.3 10.7 ± 2.2 10.8 ± 2.3 0.659

PLT (10³/µl) 264 ± 113 268 ± 116 262 ± 111 0.708

INR 1.13 ± 0.15 1.12 ± 0.10 1.14 ± 0.18 0.183

Creatinine (mg/dL) 1.08 ± 1.15 0.99 ± 1.12 1.16 ± 1.17 0.251

ALT (U/L) 41.9 ± 114 32.2 ± 45.1 51.3 ± 154 0.258

with those without a second primary cancer (87.3% vs. 73.8%; p = 0.029) (Table 2).

Bleeding and various treatment modalities

In the ED, 131 of 231 (56.7%) patients had active bleeding, while the remaining patients (n = 100, 43.3%) had self-limited bleeding. The underlying mechanisms of HNC bleeding were as follows: tumor-related (n = 183, 79.2%), pseudoaneurysm (n = 25, 10.8%), postoperative complications (n = 22, 9.5%), and fistula formation (n = 1, 0.4%). Less than half of the patients (n = 76, 32.9%) underwent emergent CT angiography to confirm the bleeder location. Of these, 7 (9.2%) patients showed contrast extravasation on imaging (7 from the external carotid artery), 19 (25%) had pseudoaneurysm (12 from the external carotid artery, 5 from the internal carotid artery, and 2 from the common carotid artery), 6 (7.9%) had pseudoaneurysm combined with contrast extravasation (5 from the external carotid artery and 1 from the internal carotid artery), and 44 (57.9%) had no identified vessel involvement.

With regard to bleeding treatment, most patients (n = 191, 82.7%) received only supportive care, while other treatments comprised transarterial embolization (n = 31, 13.4%), covered stent placement (n = 5, 2.2%), surgical ligation (n = 3, 1.3%), and primary repair (n = 1, 0.4%). In addition, 98 (42.4%) patients received blood transfusion (Table 2). The mortality rates after supportive care and transarterial embolization were 13.6% (26/191) and 12.9% (4/31), respectively. Patients who underwent covered stent placement, surgical ligation, and primary repair all survived to hospital discharge.

Rebleeding assessment in patients with HNC

Of 231 patients, 112 (48.5%) experienced a rebleeding event. The median time to rebleeding was 59 days (interquartile range [IQR] = 13–266) for those with index HNC bleeding, and 26 (23.2%) patients died after readmission. The cumulative incidence rate of rebleeding was 23% at 30 days, 49% at 180 days, and 56% at 1 year (Fig. 2). Patients with laryngeal cancer had significantly higher rebleeding rate compared with those without (75 vs. 46.5%, p = 0.028). The rebleeding rate stratified by cancer sites and BMI were presented in Table 3. We analyzed the influence of the BMI on survival by stratifying the patients into three groups based on the World Health Organization classification: underweight (< 18.5 kg/m²), normal weight (18.5 to < 25 kg/m²), and overweight-to-obesity (≥ 25 kg/m²) [16]. The overweight-to-obesity group showed the lowest cumulative rebleeding incidence curve (p = 0.012) (Fig 3). Univariate and multivariate Cox regression analyses were performed to assess factors associated with increased risk of rebleeding. Univariate predictors included overweight-to-obesity (hazard ratio [HR] = 0.44, 95% confidence interval [CI] 0.24–0.80, p = 0.007), laryngeal cancer (hazard ratio

Table 1 Characteristics of patients with head and neck cancer bleeding according to rebleeding status

| Variable                  | Total N = 231 | Rebleeding N = 112 | Non-rebleeding N = 119 | P value |
|---------------------------|---------------|--------------------|------------------------|---------|
| Age (year)                | 56.7 ± 10.9   | 55.4 ± 100         | 580.0 ± 11.5           | 0.073   |
| Male                      | 215(93.1)     | 106(94.6)          | 109(91.6)              | 0.362   |
| BMI                       | 21.5 ± 3.9    | 21.4 ± 3.9         | 21.6 ± 4.0             | 0.743   |
| Systolic blood pressure   | 139.7 ± 35.5  | 140.3 ± 34.0       | 139.2 ± 37.0           | 0.807   |
| Diastolic blood pressure  | 84.9 ± 18.2   | 85.5 ± 18.3        | 84.4 ± 18.2            | 0.643   |
| Heart rate                | 102.6 ± 22.5  | 102.4 ± 22.2       | 102.8 ± 22.9           | 0.893   |
| Smoking history           | 185(80.1)     | 96(85.7)           | 89(74.8)               | 0.038*  |
| Betel nut chewer          | 157(68.0)     | 77(68.8)           | 80(67.2)               | 0.804   |
| Hypertension              | 84(36.4)      | 38(33.9)           | 46(38.7)               | 0.455   |
| Diabetes mellitus         | 51(22.1)      | 20(17.9)           | 31(26.1)               | 0.133   |
| WBC (10³/µl)              | 11.5 ± 8.2    | 12.1 ± 10.1        | 11.0 ± 6.0             | 0.297   |
| Hb (g/dl)                 | 10.8 ± 2.3    | 10.7 ± 2.2         | 10.8 ± 2.3             | 0.659   |
| PLT (10³/µl)              | 264 ± 113     | 268 ± 116          | 262 ± 111              | 0.708   |
| INR                       | 1.13 ± 0.15   | 1.12 ± 0.10        | 1.14 ± 0.18            | 0.183   |
| Creatinine (mg/dL)        | 1.08 ± 1.15   | 0.99 ± 1.12        | 1.16 ± 1.17            | 0.251   |
| ALT (U/L)                 | 41.9 ± 114    | 32.2 ± 45.1        | 51.3 ± 154             | 0.258   |

Count data are expressed as number (percentage) and continuous values are expressed as mean ± SD

BMI: Body mass index, WBC: White blood cell, Hb: Hemoglobin, PLT: Platelet count, INR: International normalized ratio, ALT: Alanine aminotransferase

*p value < 0.05
Table 2  Features of cancer and rebleeding in patients with head and neck cancer according to rebleeding status

| Variable                      | Total N = 231 | Rebleeding N = 112 | Non-rebleeding N = 119 | P value |
|-------------------------------|---------------|--------------------|------------------------|---------|
| **Cancer site**               |               |                    |                        |         |
| Oral cavity                  | 94 (40.7)     | 41 (36.6)          | 53 (44.5)              | 0.235   |
| Nasopharynx                  | 34 (14.7)     | 16 (14.3)          | 18 (15.1)              |         |
| Oropharynx                   | 42 (18.2)     | 20 (17.9)          | 22 (18.5)              |         |
| Hypopharynx                  | 45 (19.5)     | 23 (20.5)          | 22 (18.5)              |         |
| Larynx                       | 16 (6.9)      | 12 (10.7)          | 4 (3.4)                |         |
| **Initial T stage**          |               |                    |                        | 0.371   |
| T1                            | 27 (11.7)     | 10 (8.9)           | 17 (14.3)              |         |
| T2                            | 36 (15.6)     | 21 (18.8)          | 15 (12.6)              |         |
| T3                            | 27 (11.7)     | 15 (13.4)          | 12 (10.1)              |         |
| T4                            | 131 (56.7)    | 63 (56.3)          | 68 (57.1)              |         |
| Unknown                       | 10 (4.3)      | 3 (2.7)            | 7 (5.9)                |         |
| **Initial N stage**          |               |                    |                        | 0.590   |
| N0                            | 108 (46.8)    | 52 (46.4)          | 56 (47.1)              |         |
| N+                            | 112 (48.5)    | 58 (51.8)          | 54 (45.4)              |         |
| Unknown                       | 11 (4.8)      | 2 (1.8)            | 9 (7.6)                |         |
| **Initial M stage**          |               |                    |                        | 0.116   |
| M0                            | 199 (86.1)    | 102 (91.1)         | 97 (81.5)              |         |
| M1                            | 20 (8.7)      | 7 (6.3)            | 13 (10.9)              |         |
| Unknown                       | 12 (5.2)      | 3 (2.7)            | 9 (7.6)                |         |
| **Pathology type**           |               |                    |                        | 0.540   |
| Squamous cell carcinoma      | 213 (92.2)    | 104 (92.9)         | 109 (91.6)             |         |
| Keratinizing carcinoma       | 213 (92.2)    | 104 (92.9)         | 109 (91.6)             |         |
| Nonkeratinizing carcinoma    | 16 (6.9)      | 7 (6.3)            | 9 (7.6)                |         |
| Sarcomatoid carcinoma        | 1 (0.4)       | 0 (0)              | 1 (0.8)                |         |
| Adenocarcinoma               | 1 (0.4)       | 1 (0.9)            | 0 (0)                  |         |
| **Cancer treatment**         |               |                    |                        |         |
| Surgical resection           | 117 (50.6)    | 57 (51.4)          | 60 (50.4)              | 0.888   |
| Chemoradiation               | 179 (77.5)    | 92 (82.1)          | 87 (73.1)              | 0.100   |
| Neck dissection              | 100 (43.3)    | 50 (45.0)          | 50 (42.7)              | 0.725   |
| Flap reconstruction          | 80 (34.6)     | 42 (37.8)          | 38 (32.5)              | 0.397   |
| **Local recurrence**         | 92 (39.8)     | 50 (45.0)          | 42 (36.2)              | 0.175   |
| Second primary cancer        | 63 (27.3)     | 37 (33.0)          | 26 (21.8)              | 0.056   |
| **Bleeding cause**           |               |                    |                        | 0.726   |
| Tumor-related                | 183 (79.2)    | 91 (81.3)          | 92 (78.6)              |         |
| Pseudoaneurysm               | 25 (10.8)     | 12 (10.7)          | 13 (10.9)              |         |
| Postoperative complication   | 22 (9.5)      | 9 (8)              | 13 (10.9)              |         |
| Fistula formation            | 1 (0.4)       | 0 (0)              | 1 (0.8)                |         |
| **Bleeding type**            |               |                    |                        | 0.509   |
| Self-limited                 | 100 (43.3)    | 46 (41.1)          | 54 (45.4)              |         |
| Active bleeding              | 131 (56.7)    | 66 (58.9)          | 65 (54.6)              |         |
| **Emergent CTA**             | 76 (32.9)     | 41 (36.6)          | 35 (29.4)              | 0.245   |
| **Bleeding treatment**       |               |                    |                        | 0.523   |
| Supportive care              | 191 (82.7)    | 92 (82.1)          | 99 (83.2)              |         |
| Embolization                 | 31 (13.4)     | 16 (14.3)          | 15 (12.6)              |         |
| Covered stent                | 5 (2.2)       | 1 (0.9)            | 4 (3.4)                |         |
| Surgical ligation            | 3 (1.3)       | 2 (1.8)            | 1 (0.8)                |         |
| Primary repair               | 1 (0.4)       | 1 (0.9)            | 0 (0)                  |         |
| Blood transfusion            | 98 (42.4)     | 49 (43.8)          | 49 (41.2)              | 0.692   |

Count data are expressed as number (percentage) and continuous values are expressed as mean ± SD

CTA Computed tomography angiography
[HR] = 2.20, 95% confidence interval [CI] 1.15–4.22, \( p = 0.017 \), chemoradiation (HR = 2.04, 95% CI 1.24–3.35, \( p = 0.005 \)), and second primary cancer (HR = 1.57, 95% CI 1.06–2.33, \( p = 0.026 \)). After adjustment, multivariate analysis showed that overweight-to-obesity (HR = 0.52, 95% CI 0.28–0.98, \( p = 0.043 \)), laryngeal cancer (hazard ratio [HR] = 2.13, 95% confidence interval [CI] 1.07–4.23, \( p = 0.031 \)), chemoradiation (HR = 1.49, 95% CI 1.001–2.94, \( p = 0.049 \)), and second primary cancer (HR = 1.75, 95% CI 1.13–2.70, \( p = 0.012 \)) were all statistically significant independent predictors of rebleeding risk (Table 4).

### Long-term mortality and survival analysis for patients with HNC bleeding

During a median follow-up period of 5.4 months (IQR = 1.3–27.2) after a diagnosis of HNC bleeding, 125 of 231 (54.1%) patients died. The 30-day mortality rate was 15%. The overall survival at 1, 3, and 5 years was 50%, 41%, and 35%, respectively. The median survival time was 11 months (Fig. 4). Univariate and multivariate Cox regression analyses were performed to predict long-term overall survival. Univariate predictors included underweight (HR = 2.21, 95% CI 1.48–3.28, \( p < 0.001 \),

![Cumulative incidence curves of rebleeding in patients with head and neck cancer](image)

**Table 3** The rebleeding rate in patients with head and neck cancer according to cancer sites and BMI

| Variable         | Total \( N = 231 \) | Rebleeding \( N = 112 \) | Rebleeding rate | \( P \) value |
|------------------|---------------------|--------------------------|-----------------|--------------|
| **Cancer site**  |                     |                          |                 |              |
| Oral cavity      | 94(40.7)            | 41(36.6)                 | 43.6%           | 0.220        |
| Nasopharynx      | 34(14.7)            | 16(14.3)                 | 47.1%           | 0.857        |
| Oropharynx       | 42(18.2)            | 20(17.9)                 | 47.6%           | 0.901        |
| Hypopharynx      | 45(19.5)            | 23(20.5)                 | 51.1%           | 0.694        |
| Larynx           | 16(6.9)             | 12(10.7)                 | 75.0%           | 0.028*       |
| **BMI**          |                     |                          |                 |              |
| Underweight      | 53(22.9)            | 24(21.4)                 | 45.3%           | 0.595        |
| Normal weight    | 143(61.9)           | 75(67)                   | 52.4%           | 0.124        |
| Overweight-to-obesity | 35(15.2) | 13(11.6) | 37.1% | 0.145 |

Count data are expressed as number (percentage) and continuous values are expressed as mean ± SD.

BMI: Body mass index.

*\( P \) value < 0.05
overweight-to-obesity (HR = 0.47, 95% CI 0.26–0.85, p = 0.012), heart rate > 110 beats/min (HR = 2.00, 95% CI 1.38–2.88, p < 0.001), hypopharyngeal cancer (HR = 1.83, 95% CI 1.21–2.76, p = 0.004), surgical resection (HR = 0.60, 95% CI 0.42–0.86, p = 0.005), chemoradiation (HR = 3.15, 95% CI 1.83–5.42, p < 0.001), T stage (HR = 1.36, 95% CI 1.14–1.63, p = 0.001), N stage (HR = 1.25, 95% CI 1.06–1.47, p = 0.008), local recurrence (HR = 1.93, 95% CI 1.35–2.76, p < 0.001), WBC count > 11.0 (10^{3}/µL; HR = 1.48, 95% CI 1.03–2.12, p = 0.034), and hemoglobin < 10.0 g/dL (HR = 1.90, 95% CI 1.35–2.73, p < 0.001). Multivariate analyses indicated that underweight (HR = 1.89, 95% CI 1.22–2.93, p = 0.004), heart rate > 110 beats/min (HR = 1.58, 95% CI 1.04–2.39, p = 0.032), chemoradiation (HR = 2.31, 95% CI 1.18–4.52, p = 0.015), and local recurrence (HR = 1.74, 95% CI 1.14–2.67, p = 0.011) were all statistically significant independent prognostic factors of overall survival (Table 5).

Discussion

To the best of our knowledge, this is the first cohort study to identify predictors of rebleeding in patients with HNC. The major findings of the study were as follows: (1) the rebleeding rate was 48.5%, and the median time to rebleeding was 59 days; (2) the in-hospital mortality rate was 13%, and the long-term median survival time was 11 months; (3) increased BMI (HR = 0.95, p = 0.041) was a significant independent protective factor, while chemoradiation (HR = 1.68, p = 0.049) and a second primary cancer (HR = 1.60, p = 0.023) were risk factors for increased risk of rebleeding in patients with HNC; and (4) increased BMI (HR = 0.93, p = 0.011), heart rate > 110 beats/min (HR = 1.54, p = 0.040), chemoradiation (HR = 2.35, p = 0.010), and local recurrence (HR = 1.70, p = 0.014) were significant independent prognostic factors of overall survival.

Previous studies have investigated multiple aspects of HNC bleeding, such as the bleeding rate, survival rate, and management, while the risk factors for rebleeding have not been identified. In the existing research, significant bleeding is found in 6%–14% of patients with HNC [1], and massive bleeding accounts for 6%–10% of patients with advanced HNC [4]. Acute catastrophic bleeding in the head and neck area may lead to a life-threatening situation, which involves not only hemorrhagic shock but also aspiration of blood, contributing to asphyxiation. Advanced HNC with the involvement of major vasculature implies poor prognosis, with an overall survival rate ranging from 35%–50% [12]. One of the reasons for high mortality is that management of unexpectedly massive HNC bleeding is complicated and difficult for frontline physicians. Massive bleeding necessitates immediate intervention, but it is usually hampered by hemodynamic instability, decreased visualization, and difficulty in localizing the bleeding source. Most previous studies have focused on the management of and outcome in carotid blowout syndrome (CBS) [4, 8, 17–21]. Despite the extensive research, no studies have investigated who are at increased risk of rebleeding when the first episode of HNC bleeding occurs. The reason there are no identified risk factors for HNC rebleeding is that previous studies
included a relatively small number of patients (<50) [7, 8, 11, 12, 17, 22] and could not detect an independent predictor. Additionally, CBS accounts for only a portion of HNC bleeding, and such studies may preclude a large majority of patients with HNC bleeding. Our study adds to the existing literature and will help physicians identify patients at risk in a real-world setting.

The current study identified an association between BMI and rebleeding rate as well as long-term survival rate. We found that an increased BMI is associated with a lower incidence of rebleeding events. The overweight-to-obesity group had a significantly lower cumulative event incidence curve compared with the normal weight and underweight groups. Chen et al. retrospectively reviewed patients with HNC and identified BMI < 22.5 kg/m² as an independent risk factor for CBS development; however, the authors did not investigate the effect of BMI on rebleeding risk [13]. The BMI is considered a biomarker reflecting nutritional status and is widely used since it is easy to measure precisely. Malnutrition is common in patients with advanced cancer, with a prevalence rate of 30%–85% [23]. Patients with advanced HNC tend to be malnourished, with an impaired calorie and protein balance and weakening of immune defense [24]. A poor nutritional status puts patients with HNC at an increased risk of CBS and has prognostic influence on outcomes in these patients [13, 22]. One possible explanation is that malnutrition results in less soft-tissue coverage,
with weakening arterial walls in the cervical region [22]. Another proposed mechanism is the interaction between nutritional status and the immune system [25]. Malnutrition reduces the resistance to infection by depressing the immune system and may further trigger a vicious cycle, exacerbating the poor nutritional status and inflammatory process. These combined effects render the carotid artery or its branches vulnerable to vasa vasorum thrombosis, poor intravascular wound healing, and arterial wall injury [22, 26]. In this study, a decreased BMI was also a predictive factor of poor long-term overall survival in patients with HNC bleeding. One large prospective cohort study by Gama et al. demonstrated that underweight is an adverse prognostic factor, while overweight has better prognosis in patients with HNC [24]. Underweight patients may have more comorbidities, an advanced cancer stage, and poorer nutritional status. They also tend to have lower tolerance to the toxicities of cancer treatment [24, 27]. As shown in this study, the adverse impact of a low BMI exerts an additive effect, with acute hemorrhage in patients with HNC, leading to a worse overall survival.

Our study demonstrated that chemoradiation and a second primary cancer were associated with an increased risk of rebleeding. Although chemotherapy and radiotherapy limit cancer progression and prolong the life expectancy of patients with HNC, they are also accompanied by an up to 7.6 times higher risk of bleeding [5]. Studies have indicated that radiotherapy results in upregulation of pro-inflammatory cytokines and inflammatory cells are recruited to the area of vascular injury [28, 29]. Radiation causes further free-radical production and oxidative stress in affected tissues, contributing to thrombosis and obliteration of the adventitial vasa vasorum, adventitial fibrosis, premature atherosclerosis, and arterial wall weakening [7]. Chemotherapy-induced vascular toxicity is frequently secondary to endothelial dysfunction, which manifests as a loss of vasorelaxant effects and reduced anti-inflammatory as well as vascular reparative functions [30]. These effects make the carotid artery more vulnerable to necrosis or rupture due to ischemia [5, 28]. In addition, patients with a second primary cancer usually require re-irradiation with or without chemotherapy [31]. They may receive cumulative radiation doses totaling over 200% of the tolerance of normal tissues [32]. Re-irradiation exposes these tissues to considerable toxicity and thereby leads to a higher risk of hemorrhage [5]. A recent longitudinal study by Jacobi et al. revealed that chemotherapy is related to an increased risk of CBS development [7]. However, our study showed that not only chemoradiation but also a second primary cancer contributes to a significantly higher risk of rebleeding in patients with HNC. Our study found that patients with laryngeal cancer were significantly more likely to have rebleeding than those with HNC at other sites. We speculate that advanced laryngeal cancer requiring multiple treatments makes blood vessels more vulnerable to side effects and results in massive hemorrhage owing to blood vessel damages in the infiltrated region.

Our identification of local recurrence and chemoradiation as two other risk factors for long-term survival is consistent with the prior studies that reported the association between these factors and worse long-term survival in patients with CBS [7, 22]. Despite being at an advanced
cancer stage, patients with local recurrence may need more cancer-related treatment, such as chemoradiation or operative resection, which poses an increased risk of bleeding and affects survival outcomes. Patients with HNC can present with self-limited episodes of minor bleeding followed by subsequent massive bleeding and cardiovascular collapse within hours. It is important to note that tachycardia, rather than hypotension, is an independent significant risk factor for mortality as the value of blood pressure tends to be influenced by the vessel constriction and physiological compensation—which can mask the real hemodynamic status—in the early stage of hypovolemic shock [33]. Aggressive fluid resuscitation and inotropes are the mainstay of medical therapy to restore normo-tension and reduce tachycardia. Prolonged volume depletion places patients at great risk of high morbidity and mortality since decreased cardiac output leads to insufficient tissue oxygenation that may cause multiorgan failure [34].

**Limitations**

This study had several limitations. First, the study design, as a retrospective chart review, did not allow for uniform collection of all clinical variables. For example, accurate total chemoradiation dosing data were not available in one-third of our patients, limiting our analysis of the association between doses and rebleeding risk. Second, although we used the BMI as an anthropometric proxy for nutritional status, it does not consider body fat distribution, cardiorespiratory status, or other health factors like sarcopenia does. Third, this was a single-country study design.

### Table 5

Univariate and multivariate analyses of predictors for long-term survival with Cox proportional hazards model

|                      | Univariate          | Multivariate         |
|----------------------|----------------------|----------------------|
|                      | HR(95%CI)            | P value              | HR(95%CI)            | P value |
| Age                  | 0.99(0.97,1.003)     | 0.986                |                      |         |
| Male                 | 0.81(0.42,1.54)      | 0.517                |                      |         |
| BMI                  |                      |                      |                      |         |
| Underweight          | 2.21(1.48,3.28)      | < 0.001              | 1.89(1.22,2.93)      | 0.004*  |
| Normal weight        | Reference            |                      | Reference            |         |
| Overweight-to-obesity| 0.47(0.26,0.85)      | 0.012                | 0.75(0.39,1.43)      | 0.379   |
| Cancer site          |                      |                      |                      |         |
| Oral cavity          | Reference            | 0.312                | Reference            | 0.881   |
| Nasopharynx          | 1.31(0.77,2.23)      | 0.373                | 0.95(0.47,1.90)      | 0.664   |
| Oropharynx           | 1.26(0.76,2.11)      | 0.012                | 1.14(0.63,2.07)      | 0.179   |
| Hypopharynx          | 2.04(1.28,3.25)      | 0.003                | 1.43(0.85,2.40)      | 0.342   |
| Larynx               | 0.98(0.46,2.09)      | 0.965                | 0.65(0.30,1.44)      | 0.291   |
| Smoking history      | 1.09(0.69,1.73)      | 0.712                |                      |         |
| SBP < 90 (mmHg)      | 1.76(0.95,3.28)      | 0.074                |                      |         |
| Heart rate > 110 (beats/min) | 2.00(1.38,2.88) | < 0.001              | 1.58(1.04,2.39)      | 0.032*  |
| Hypertension         | 0.72(0.49,1.04)      | 0.082                |                      |         |
| Diabetes mellitus    | 0.77(0.50,1.19)      | 0.235                |                      |         |
| Surgical resection   | 0.60(0.42,0.86)      | 0.005                | 0.86(0.53,1.39)      | 0.856   |
| Chemoradiation       | 3.15(1.83,5.42)      | < 0.001              | 2.31(1.18,4.52)      | 0.015*  |
| Neck dissection      | 0.88(0.62,1.26)      | 0.495                |                      |         |
| Flap reconstruction  | 0.96(0.66,1.39)      | 0.813                |                      |         |
| T stage              | 1.36(1.14,1.63)      | 0.001                | 1.16(0.94,1.42)      | 0.162   |
| N stage              | 1.25(1.06,1.47)      | 0.008                | 1.11(0.90,1.37)      | 0.337   |
| M stage              | 1.76(0.94,3.29)      | 0.075                |                      |         |
| Local recurrence     | 1.93(1.35,2.76)      | < 0.001              | 1.74(1.14,2.67)      | 0.011*  |
| Second primary cancer| 1.37(0.93,2.00)      | 0.108                |                      |         |
| WBC > 11.0 (10^3/µl) | 1.48(1.03,2.12)      | 0.034                | 1.31(0.88,1.96)      | 0.190   |
| Hb < 10.0 (g/dl)     | 1.90(1.35,2.73)      | < 0.001              | 1.15(0.75,1.76)      | 0.530   |
| PLT < 150 (10^3/µl)  | 1.22(0.76,1.96)      | 0.401                |                      |         |

*HR Hazard ratio, 95% CI 95% Confidence interval

* P value < 0.05
study, and race as well as ethnicity in Taiwan is relatively homogenous. Further prospective multicountry studies are necessary to strengthen our findings.

Conclusion
Overweight-to-obesity is a protective factor, while laryngeal cancer, chemoradiation and a second primary cancer are risk factors for rebleeding in patients with HNC. Our results may play a pivotal role in assisting physicians in risk stratification and better decision making for patients with HNC with life-threatening bleeding.

Acknowledgements
The authors would like to express their gratitude to Chang Gung Memorial Hospital, which supported the APC.

Authors' contributions
Conceptualization: Chieh-Ching Yen and Chih-Kai Wang; Data curation: Chih-Kai Wang and Che-Fang Ho; Formal analysis: Chieh-Ching Yen; Investigation: Yun-Chen Chang and Chia-Chien Wu; Resources: Kuang-Yu Niu and Chien-Han Hsiao; Supervision: Chieh-Ching Yen; Writing – original draft: Chih-Kai Wang. All authors have read and agreed to the published version of the manuscript.

Funding
This research received no external funding.

Availability of data and materials
The datasets generated and analyzed during the current study are not publicly available due to restrictions but are available from the corresponding author on reasonable request.

Declarations
Ethics approval and consent to participate
The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board of Chang Gung Medical Foundation (IRB no. 202102021B0, Date of Approval: 2021/12/03). The need for written informed consent was waived by the Chang Gung Medical Foundation (IRB no. 202102021B0, Date of Approval: 2021/12/03). The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board of Chang Gung Medical Foundation (IRB no. 202102021B0, Date of Approval: 2021/12/03). The need for written informed consent was waived by the Chang Gung Medical Foundation (IRB no. 202102021B0, Date of Approval: 2021/12/03).

Consent for publication
Not applicable.

Competing interests
The authors declare no Competing Interests.

Author details
1Department of Emergency Medicine, Linkou Branch, Chang Gung Memorial Hospital, Taoyuan, Taiwan. 2Department of Otolaryngology Head and Neck Surgery, Chang Gung Memorial Hospital, Keelung, Taiwan. 3Department of Emergency Medicine, Keelung Branch, Chang Gung Memorial Hospital, Keelung, Taiwan. 4Department of Medical Imaging and Intervention, Linkou Branch, Chang Gung Memorial Hospital, Taoyuan, Taiwan. 5Department of Otolaryngology Head and Neck Surgery, Linkou Branch, Chang Gung Memorial Hospital, Taoyuan, Taiwan. 6Department of Linguistics, Indiana University, Bloomington, IN, USA. 7Institute of Emergency and Critical Care Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan.

Received: 1 June 2022   Accepted: 28 July 2022
Published online: 02 August 2022

References
1. Vilas Boas PP, de Castro-Afonso LH, Monsignore LM, Nakiri GS, de Mello-Filho VF, Abud DG. Endovascular Management of Patients with Head and Neck Cancers Presenting with Acute Hemorrhage: A Single-Center Retrospective Study. Cardiovasc Intervent Radiol. 2017;40(4):510–9.
2. Miller T, Burns J, Farinhas J, Pasquale D, Haboobeh A, Bello JA, Brook A. Covered stents safely utilized to prevent catastrophic hemorrhage in patients with advanced head and neck malignancy. J Neurointerv Surg. 2012;4(6):426–34.
3. Lee JJ, Jeng JH, Wang HM, Chang HH, Chiang CP, Kuo YS, Lan WH, Kok SH. Univariate and multivariate analysis of prognostic significance of betel quid chewing in squamous cell carcinoma of buccal mucosa in Taiwan. J Surg Oncol. 2005;91(1):41–7.
4. Lu H-J, Chen K-W, Chen M-H, Chu P-Y, Tai S-K, Wang L-W, Chang PM-H, Yang M-H. Predisposing factors, management, and prognostic evaluation of acute carotid blowout syndrome. J Vasc Surg. 2013;58(5):1226–33.
5. Suárez C, Fernández-Alvarez V, Hamoir M, Mendenhall WM, Strojan P, Quer M, Silver CE, Rodrigo JP, Rinaldo A, Ferlito A. Carotid blowout syndrome: modern trends in management. Cancer Management and Research. 2018;10:5617–28.
6. Shah H, Gemmette JJ, Chaudhary N, Pandey AS, Ansari SA. Acute life-threatening hemorrhage in patients with head and neck cancer presenting with carotid blowout syndrome: follow-up results after initial hemostasis with covered-stent placement. AJNR Am J Neuroradiol. 2011;32(4):743–7.
7. Jacobi C, Gahleitner C, Bier H, Knoop F. Chemoradiation and local recurrence of head and neck squamous cell carcinoma and the risk of carotid artery blowout. Head Neck. 2019;41(9):3073–9.
8. Liang NL, Guedes BD, Duvvuri U, Singh MJ, Chaer RA, Makatoun M, Sachdev U. Outcomes of interventions for carotid blowout syndrome in patients with head and neck cancer. J Vasc Surg. 2016;63(6):1525–30.
9. Recka K, Montagnini M, Vitale CA. Management of bleeding associated with malignant wounds. J Palliat Med. 2012;15(8):952–4.
10. Harris DG, Noble SJ. Management of terminal hemorrhage in patients with advanced cancer: a systematic literature review. J Pain Symptom Manage. 2009;38(6):913–27.
11. Xu X, Ding YK, Loh WS, Anil G, Yap QV, Loh KS. Clinical predictors of internal carotid artery blowout in patients with radiated nasopharyngeal carcinoma. Head Neck. 2021;43(12):3757–63. https://doi.org/10.1002/hed.26869.
12. Krol E, Brandt CT, Blakeslee-Carter J, Ahanchi SS, Dexter DJ, Karakla D, Panneton JM. Vascular interventions in head and neck cancer patients as a marker of poor survival. J Vasc Surg. 2019;69(1):181–9.
13. Chen YJ, Wang CP, Wang CC, Jiang RS, Lin JC, Liu SA. Carotid blowout in patients with head and neck cancer: associated factors and treatment outcomes. Head Neck. 2015;37(2):265–72.
14. Yen C-C, Ho C-F, Wu C-C, Tsao Y-N, Chao C-H, Chen S-Y, Ng C-J, Yeh H. In-Hospital and Long-Term Outcomes in Patients with Head and Neck Cancer Bleeding. Medicina. 2022;58(2):177.
15. Yen CC, Yeh H, Ho CF, Hsiao CH, Niu KY, Yeh CC, Lu JX, Wu CC, Chang YC, Ng C-J. Risk factors for 30-day mortality in patients with head and neck cancer bleeding in the emergency department. Am J Emerg Med. 2022;58:9–15.
16. Obesity and overweight [https://www.who.int/news-room/fact-sheets/ topic/obesity-and-overweight]. Accessed 9 June 2021.
17. Chang F-C, Lin M-J, Lee C-F, Lin E-H, Wu H-M, Guo W-Y, Teng MMH, Chang C-Y. Patients with head and neck cancers and associated postirradiated carotid blowout syndrome: Endovascular therapeutic methods and outcomes. J Vasc Surg. 2008;47(5):936–45.
18. Wong DJY, Donaldson C, Lai LT, Coleman A, Giddings C, Slater LA, Chandaria RV. Safety and effectiveness of endovascular embolization or stent-graft reconstruction for treatment of acute carotid blowout syndrome in patients with head and neck cancer: Case series and systematic review of observational studies. Head Neck. 2018;40(4):846–54.
19. Wu CJ, Lin WC, Hsu JS, Han IT, Hsieh TJ, Liu GC, Chang IC. Follow-up for covered stent treatment of carotid blow-out syndrome in patients with head and neck cancer. Br J Radiol. 2016;89(1058):20150136.
20. Chang FC, Luo CB, Lirng JF, Lin CJ, Lee HJ, Wu CC, Hung SC, Guo WY. Endovascular Management of Post-Irradiated Carotid Blowout Syndrome. PLoS ONE. 2015;10(10):e0139821.
21. Lee CW, Yang CY, Chen YF, Huang A, Wang YH, Liu HM. CT angiography findings in carotid blowout syndrome and its role as a predictor of 1-year survival. AJNR Am J Neuroradiol. 2014;35(3):562–7.

22. Lu HJ, Chen KW, Chen MH, Chu PY, Tai SK, Tseng CH, Chang PM, Yang MH. Serum albumin is an important prognostic factor for carotid blowout syndrome. Jpn J Clin Oncol. 2013;43(5):532–9.

23. Nakayama M, Gosho M, Adachi M, Ii R, Matsumoto S, Miyamoto H, Hirose Y, Nishimura B, Tanaka S, Wada T, et al. The Geriatric Nutritional Risk Index as a Prognostic Factor in Patients with Advanced Head and Neck Cancer. Laryngoscope. 2021;131(1):E151–e156.

24. Gama RR, Song Y, Zhang Q, Brown MC, Wang J, Habbous S, Tong L, Huang SH, O’Sullivan B, Waldron J, et al. Body mass index and prognosis in patients with head and neck cancer. Head Neck. 2017;39(6):1226–33.

25. Shirasu H, Yokota T, Hamauchi S, Onozawa Y, Ogawa H, Onee T, Onitsuka T, Yunkusa T, Mori K, Yasui H. Risk factors for aspiration pneumonia during concurrent chemoradiotherapy or bio-radiotherapy for head and neck cancer. BMC Cancer. 2020;20(1):182.

26. Bergamini C, Ferris RL, Xie J, Mariani G, Ali M, Holmes WC, Harrington K, Pyrri A, Cavaliere S, Licitra L. Bleeding complications in patients with squamous cell carcinoma of the head and neck. Head Neck. 2021;43(9):2844–58. https://doi.org/10.1002/hed.26772.

27. Wu EL, Peesay T, Randall JA, Nelson LL, Shearer SC, Johnson BC, Maxwell JH. Increased body mass index predicts prolonged survival in patients with head and neck squamous cell carcinoma. Head Neck. 2022;44(2):325–31. https://doi.org/10.1002/hed.26922.

28. Venkatesulu BP, Mahadevan LS, Aliru ML, Yang X, Bodd MH, Singh PK, Yusuf SW, Abe J, Krishnan S. Radiation-Induced Endothelial Vascular Injury: A Review of Possible Mechanisms. JACC Basic Transl Sci. 2018;3(4):563–72.

29. Weintraub NL, Jones WK, Manka D. Understanding radiation-induced vascular disease. J Am Coll Cardiol. 2010;55(12):1237–9.

30. Cameron AC, Touyz RM, Lang NN. Vascular Complications of Cancer Chemotherapy. Can J Cardiol. 2016;32(7):852–62.

31. Vargo JA, Ward MC, Caudell JJ, Riaz N, Dunlap NE, Isrow D, Zakem SJ, Dautt J, Awan MJ, Higgin KA, et al. A Multi-institutional Comparison of SBRT and IMRT for Definitive Reirradiation of Recurrent or Second Primary Head and Neck Cancer. Int J Radiat Oncol Biol Phys. 2018;100(3):595–605.

32. Self EM, Bumpous J, Ziegler C, Wilson L, Potts K. Risk Factors for Hemorrhage After Chemoradiation for Oropharyngeal Squamous Cell Carcinoma. JAMA Otolaryngology-Head & Neck Surgery. 2013;139(4):356.

33. Cannon JW. Hemorrhagic Shock. N Engl J Med. 2018;378(4):370–9.

34. Yo CH, Lai CC, Hsu TC, Wang CY, Galvin AE, Yen D, Hsu WT, Wang J, Lee CC. National Trends of Organ Dysfunctions in Sepsis. An 11-Year Longitudinal Population-Based Cohort Study. J Acute Med. 2019;9(4):178–88.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.