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Serum Albumin is an Important Prognostic Factor for Carotid Blowout Syndrome

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Objective: Carotid blowout syndrome is a severe complication of head and neck cancer. High mortality and major neurologic morbidity are associated with carotid blowout syndrome with massive bleeding. Prediction of outcomes for carotid blowout syndrome patients is important for clinicians, especially for patients with the risk of massive bleeding.
Methods: Between 1 January 2001 and 31 December 2011, 103 patients with carotid blowout syndrome were enrolled in this study. The patients were divided into groups with and without massive bleeding. Prognostic factors were analysed with proportional hazard (Cox) regressions for carotid blowout syndrome-related prognoses. Survival analyses were based on the time from diagnosis of carotid blowout syndrome to massive bleeding and death.
Results: Patients with massive bleeding were more likely to have hypoalbuminemia (albumin <3.5 g/dl; $P = 0.023$). Univariate analysis of carotid blowout syndrome-related massive bleeding showed that treatment for carotid blowout syndrome (best supportive care, $P = 0.000$; embolization, $P = 0.000$), monocytosis (monocytes >1000 cells/μl, $P = 0.041$) and hypoalbuminemia ($P = 0.010$) were important to prognosis. Concurrent chemoradiotherapy ($P = 0.007$), elevated lactate dehydrogenase (>250 U/l; $P = 0.050$), local recurrence ($P = 0.022$) and hypoalbuminemia ($P = 0.038$) were related to poor prognosis in carotid blowout syndrome-related death. In multivariate analysis, best supportive care and hypoalbuminemia were independent factors for both carotid blowout syndrome-related massive bleeding ($P = 0.000$) and carotid blowout syndrome-related death ($P = 0.013$), respectively.
Conclusion: Best supportive care and serum albumin are important prognostic factors in carotid blowout syndrome. It helps clinicians to evaluate and provide better supportive care for these patients.

Key words: head and neck cancer – carotid blowout syndrome – prognostic factor – serum albumin

INTRODUCTION

Carotid blowout syndrome (CBS)—a severe complication of head and neck cancer (HNC)—is defined either as an episode of acute hemorrhage or as exposure of a portion of the carotid arterial system (1). All HNC patients are treated in a multidisciplinary manner, relying on surgery, radiation therapy, chemotherapy and concomitant chemoradiotherapy. During the course of treatment, 3–5% of patients experience CBS (2). There are three subtypes of CBS: threatened, impending and acute CBS (1). Threatened CBS is defined as a visibly exposed carotid artery secondary to wound breakdown resulting from prior radical neck dissection or flap

mobilization. If the vessel is not promptly covered with healthy, well-vascularized tissue, it will very likely rupture. Impending CBS refers to transient carotid hemorrhage that resolves spontaneously or with simple surgical packing. The hemorrhage usually occurs through a surgical wound or fistula. Because there is no real wall with supporting structural elements in the carotid artery, complete rupture is a certainty and may occur at any time. Acute CBS is defined as an acute rupture of the extracranial carotid arteries that is not self-limiting (1). Emergent surgical or endovascular approaches for acute CBS are the standard treatments for life saving now. However, even with effective endovascular treatment (3), CBS still has high mortality and major neurologic morbidity (about 40 and 60%, respectively) (1).

As shown in Fig. 1, CBS is usually observed in HNC patients with radiation-induced necrosis, recurrent tumor, wound complications or pharyngocutaneous fistulae (1). The above local conditions are associated with the progression of underlying disease and locally tissue inflammation, which infuse the vessel healing (4). Previous studies have shown that serum albumin is an important factor for cancer prognosis and tissue inflammation (5–7). Therefore, we evaluated the serum albumin level as the prognostic factor of CBS outcome. Besides, massive bleeding from CBS is a suffering event for patients and their families. For clinicians, it is also the difficult complication to manage and most patients have the risk of unexpectedly massive bleeding. These events are typically life threatening and require advanced cardiac life support (ACLS). Partial impending CBS and all acute CBS patients are susceptible to this condition. Although aggressive resuscitation has become the standard response to this potentially lethal complication (2), the psychological burdens resulting from massive bleeding have lasting effects on patients and their families. In addition, CBS with massive bleeding is often accompanied with re-bleeding, cerebrovascular events and aspiration pneumonia (8). These complications clearly also influence patient outcomes. Therefore, we divide patients into with/without massive bleeding to identify the factors of massive bleeding. It is important to know when carotid artery rupture is likely to occur and how to prevent this complication. Apart from being useful in clinical practice, prevention of rupture will also decrease the psycho-economic burdens of patients and their families.

We analysed the factors associated with the occurrence and prognosis of CBS. The purpose was to improve prediction of massive bleeding and related deaths. With this retrospective study, we aim to manage this complication better and provide improved supportive care.

PATIENTS AND METHODS

Study Design, Setting and Patient Selection

This was a single institute, retrospective, case–control study. It was reviewed and approved by the Institutional Review Board of Taipei Veterans General Hospital (No. 2012-05-040AC). Patients who suffered CBS between 1 January 2001 and 31 December 2011 were enrolled in the study. CBS is defined as either an episode of acute hemorrhage or exposure of a portion of the carotid arterial system (1). Therefore, patients were divided into two groups: those with and those without episodes of massive bleeding. Event of massive bleeding was defined as acute, profuse hemorrhage without self-limiting over the carotid trunk (1) or bleeding episodes in which aggressive resuscitations, such as ACLS, were needed.

Characteristic data including age, gender, primary tumor information and initial TNM staging were recorded. To identify the risk factors associated with CBS, we retrospectively reviewed neck conditions, and local recurrence from the time of CBS diagnosed backwards for 6 months. Because the treatments for HNC patients are multidisciplinary team work, all treatments might be carried out in a short period. It

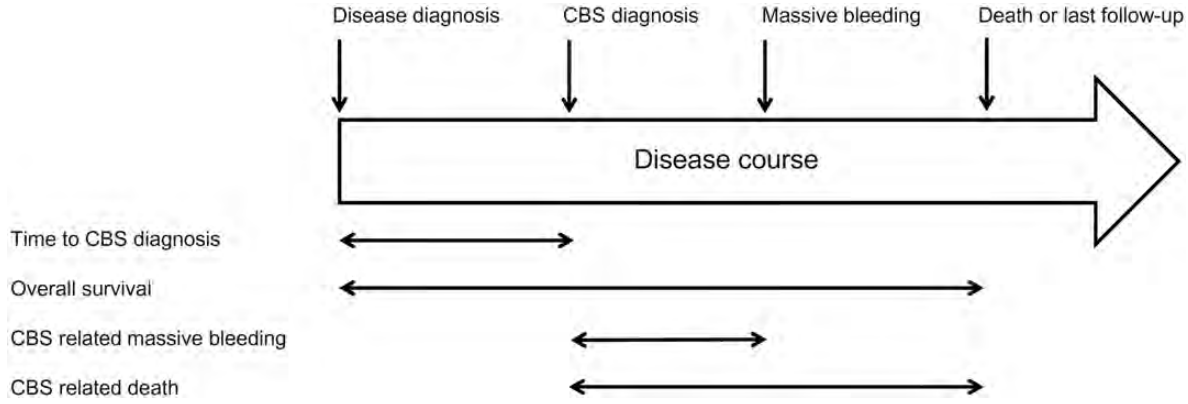

Figure 1. Disease course and carotid blowout syndrome (CBS). CBS could happen during the whole disease course after definite diagnosis. Some of them were accompanied or followed with the episode of massive bleeding. Death may be related to CBS with or without massive bleeding during follow-up. Time to CBS diagnosis: from the date of underlying malignancy diagnosis to the date of CBS diagnosis. Overall survival: from the date of disease diagnosis to date of death by any cause, or the date on which the patient was last evaluated, CBS-related massive bleeding: from the time of CBS diagnosis to the date of massive bleeding, CBS-related death: from the date of CBS diagnosis to the date of death or the date on which the patient was last evaluated. CBS, carotid blowout syndrome.

Table 1. Basic characteristics of 103 carotid blowout syndrome patients

Variable	Patients with massive bleeding ($n = 53$)	Patients without massive bleeding ($n = 50$)	*P* value
Age (years)			0.885
Median	54.4	52.3	
Range	28.1–83.7	28.4–91.5	
Gender			0.408
Male	47 (88.7%)	46 (92.0%)	
Female	6 (11.3%)	4 (8.0%)	
Location of primary tumor			0.547
Left	25 (47.2%)	22 (44.0%)	
Right	25 (47.2%)	26 (52.0%)	
Intermediate	0 (0.0%)	1 (2.0%)	
Unknown[a]	3 (5.7%)	1 (2.0%)	
Site of primary tumor			0.668
Oral cavity	10 (18.9%)	10 (20.0%)	
Nasopharynx	6 (11.3%)	6 (12.0%)	
Oropharynx	10 (18.9%)	15 (30.0%)	
Hypopharynx	20 (37.7%)	13 (26.0%)	
Larynx	4 (7.5%)	2 (4.0%)	
Others[b]	3 (5.7%)	4 (8.0%)	
Pathologic type			0.535
Squamous cell carcinoma	43 (81.1%)	41 (82.0%)	
Adenosquamous carcinoma	1 (1.9%)	0 (0.0%)	
Non-keratinizing carcinoma	5 (9.4%)	5 (10.0%)	
Sarcoma	2 (3.8%)	0 (0.0%)	
Carcinoma, undifferentiated	2 (3.8%)	0 (0.0%)	
Adenocarcinoma	0 (0.0%)	1 (2.0%)	
Adenoid cystic carcinoma	0 (0.0%)	1 (2.0%)	
Papillary carcinoma	0 (0.0%)	1 (2.0%)	
Sarcomatoid squamous cell carcinoma	0 (0.0%)	1 (2.0%)	
Initial T staging			0.625
T0	2 (3.8%)	0 (0.0%)	
T1	3 (5.7%)	6 (12.0%)	
T2	10 (18.9%)	10 (20.0%)	
T3	12 (22.6%)	9 (18.0%)	
T4	22 (41.5%)	22 (44.0%)	
Unknown[a]	7 (7.5%)	3 (6.0%)	
Initial N staging			0.327
N0	15 (28.3%)	19 (38.0%)	
N1	9 (17.0%)	5 (10.0%)	
N2	20 (37.7%)	18 (36.0%)	
N3	3 (5.7%)	6 (12.0%)	
Unknown[a]	6 (11.3%)	2 (4.0%)	
Initial M staging			0.151
M0	44 (83.0%)	47 (94.0%)	
M1	3 (5.7%)	2 (4.0%)	
Unknown[a]	6 (11.3%)	1 (2.0%)	
Latest treatment for CBS			0.689
Chemotherapy alone	17 (32.1%)	12 (24.0%)	
Radiotherapy alone	0 (0.0%)	1 (0.0%)	
Concurrent chemoradiotherapy	10 (18.9%)	10 (20.0%)	
Neck dissection	10 (18.9%)	8 (16.0%)	
Clinical follow-up	16 (30.2%)	19 (38.0%)	
Neck condition from CBS diagnosed backward for 6 months			
Wound infection	13 (24.5%)	14 (28.0%)	0.430
Fistula formation	6 (11.3%)	6 (12.0%)	0.578
Tissue necrosis	23 (43.4%)	24 (48.0%)	0.393
Vessel exposure	5 (9.4%)	2 (4.0%)	0.243
Local recurrence from CBS diagnosed backwards for 6 months	34 (64.2%)	32 (64.0%)	0.575
Serum marker at CBS diagnosis			
White blood count ($\times 10^3$ cells/μl)			0.059
No. of patients with white blood count >10.0	28 (52.8%)	17 (35.4%)	
No. of patients detected	53	48	
Monocytes (cells/μl)			0.115
No. of patients with monocytes >1000	10 (19.6%)	4 (8.9%)	
No. of patients detected	51	45	
Hemoglobin (g/dl)			0.079
No. of patients with hemoglobin <11.0	40 (75.5%)	29 (60.4%)	
No. of patients detected	53	48	
PLT ($\times 10^3$ cells/μl)			0.275
No. of patients with PLT >400.0	16 (30.2%)	11 (22.9%)	
No. of patients detected	53	48	
Albumin (g/dl)			0.023
No. of patients with albumin <3.5	28 (73.7%)	18 (48.6%)	

Table 1. *Continued*

Variable	Patients with massive bleeding ($n = 53$)	Patients without massive bleeding ($n = 50$)	P value
No. of patients detected	38	37	
Corrective Ca (mg/dl)			0.364
No. of patients with corrective Ca >10.5	3 (8.1%)	1 (3.1%)	
No. of patients detected	37	32	
LDH (U/l)			0.315
No. of patients with LDH > 250	8 (32%)	6 (22.2%)	
No. of patients detected	25	27	
ALK-p (U/l)			0.201
No. of patients with ALK-p > 100	15 (53.6%)	10 (38.5%)	
No. of patients detected	28	26	
CRP (mg/dl)			0.222
No. of patients with CRP >5	26 (70.3%)	15 (57.7%)	
No. of patients detected	37	26	

[a]Unknown cases were because they were diagnosed at other hospitals without initial data.
[b]Including carcinoma of unknown primary, ethmoid sinus cancer, nasal antrum cancer, thyroid cancer, esophagus cancer and major salivary gland cancer.

is difficult to divide patients into the certain treatment such as surgery, radiotherapy, chemotherapy and salvage therapy. And the influence/formation of CBS could not be classified as single treatment related. So we divided CBS patients into with/without massive bleeding and see the differences between their primary cites or the latest treatments before CBS such as chemotherapy alone, radiotherapy alone, current chemoradiotherapy, neck dissection or clinical follow-up. The treatments for CBS were included in the further analysis. All laboratory data, such as serum levels of albumin, corrected calcium, LDH, alkaline phosphatase (ALK-p), C-reactive protein (CRP) and complete blood counts/differential counts, were also collected at the latest time before CBS diagnosis (9, 10).

Survival Analysis

Survival analysis time periods are defined in Fig. 1. Time to CBS diagnosis was calculated from the date of underlying malignancy diagnosis to the date of CBS diagnosis. Overall survival was calculated from the date of disease diagnosis to date of death by any cause, or the date on which the patient was last evaluated. Time to CBS-related massive bleeding was calculated from the time of CBS diagnosis to the date of massive bleeding. CBS-related death was calculated from the date of CBS diagnosis to the date of death or the date on which the patient was last evaluated. The last follow-up date of all patients was 31 May 2012.

Statistical Analysis

Categorical variables were compared using the χ^2 and Fisher's exact tests. Continuous variables were compared using the Mann–Whitney test. Univariate and multivariate Cox regressions were used to analyse prognostic factors. The factors with $P < 0.05$ in univariate analyses were included in forward stepwise multivariate Cox regressions. Kaplan–Meier plots were used with log-rank tests. All statistical analyses were performed using the SPSS statistical software version 19.0 (SPSS, Chicago, IL, USA). In all the analyses, $P < 0.05$ was considered statistically significant.

RESULTS

Patient Characteristics

Between 1 January 2001 and 31 December 2011, 103 patients with CBS were enrolled in this study. Between 1 January 2001 and 31 December 2011, there were 3504 patients with newly diagnosed head and neck cancer in our institution. One hundred and three patients (103/3504, 2.9%) who suffered from CBS were identified by imaging/operation records and enrolled in this study. They were divided into groups of patients with massive bleeding and those without. Most CBS patients were under the status of local recurrence (64.2 and 64.0% in patients with/without massive bleeding, respectively). And both CBS groups have neck conditions (wound infection, fistula formation, tissue necrosis, vessel exposure) within 6 months before CBS diagnosis. The median age, gender and primary tumor site were similar to those of the CBS (−) patients. Patient characteristic data are presented in Table 1. With the exception of serum albumin levels, both groups were similar in underlying malignancies, initial TNM stage, treatment programs, neck conditions, local recurrence and other serum markers. Hypoalbuminemia was more common in the group with massive bleeding (73.7 vs. 48.6%; $P = 0.023$).

Prognostic Factors for CBS

Univariate analyses of CBS-related massive bleeding revealed that treatment for CBS (best supportive care, $P = 0.000$; embolization, $P = 0.000$), monocyte counts of >1000 (cells/μl) ($P = 0.041$) and albumin levels <3.5 (g/dl) ($P = 0.010$) were important. Multivariate analyses indicated that only treatment for CBS with best supportive care was an independent factor [hazard ratio, 10.042; 95% confidence interval (CI), 4.090–24.657; $P < 0.000$] (Table 2).

Table 2. Univariate and multivariate Cox regression analysis of the predicting factor for CBS-related massive bleeding

Variable	Univariate[a]		Multivariate	
	P value	HR (95% CI)	*P* value	HR (95% CI)
Male	0.715			
Age >65 years	0.467			
Initial disease status				
T stage >2	0.581			
N stage >0	0.379			
Latest treatment for CBS				
Chemotherapy alone	0.517			
Radiotherapy alone	0.600			
Concurrent chemoradiotherapy	0.845			
Neck dissection	0.586			
Clinical follow-up	0.316			
Neck condition from CBS diagnosed backward for 6 months				
Wound infection	0.682			
Fistula formation	0.832			
Tissue necrosis	0.713			
Vessel exposure	0.504			
Treatment for CBS-related massive bleeding				
None	0.000	5.773 (2.928–11.380)	0.000	10.042 (4.090–24.657)
Stent insertion	0.519			
Embolization	0.000	0.181 (0.072–0.457)		
Stent insertion and embolization	0.102			
Surgical ligation	0.688			
Local recurrence from CBS diagnosed backward for 6 months	0.784			
Serum marker at CBS diagnosis				
White blood count >10.0 × 10^3 (cells/μl)	0.076			
Monocytes >1000 (cells/μl)	0.041	2.087 (1.029–4.235)		
Hemoglobin <11.0 (g/dl)	0.091			
PLT >400 × 10^3 (cells/μl)	0.244			
Albumin <3.5 (g/dl)	0.010	2.644 (1.257–5.563)		
Corrective Ca >10.5 (mg/dl)	0.512			
LDH >250 U/l	0.425			
ALK-p > 100 U/l	0.382			
CRP >5 (mg/dl)	0.256			

CBS, carotid blowout syndrome; HR, hazard ratio; CI, confidence interval.
[a]The factors with $P < 0.05$ in univariate analysis were included in the forward stepwise multivariate Cox hazard regression.

Univariate analysis of CBS-related death revealed that concurrent chemoradiotherapy ($P = 0.007$), local recurrence ($P = 0.022$), albumin <3.5 g/day ($P = 0.038$) and LDH >250 U/l ($P = 0.050$) were important factors; hypoalbuminemia (albumin <3.5 g/day; HR, 3.084; 95% CI, 1.267–7.510) was an independent prognostic factor for CBS-related death (Table 3).

Kaplan–Meier Plots for Prognostic Factors

As shown in Fig. 2, hypoalbuminemia and monocytosis were significant in univariate analysis. Kaplan–Meier plots revealed that hypoalbuminemia ($P = 0.005$) and monocytosis ($P = 0.024$) could effectively predict massive bleeding. In addition, hypoalbuminemia, LDH >250 U/l and local

Table 3. Univariate and multivariate Cox regression analysis of the prognostic factor for CBS-related death

Variable	Univariate[a]		Multivariate	
	P value	HR (95% CI)	*P* value	HR (95% CI)
Male	0.789			
Age >65 years	0.502			
Initial disease status				
T stage >2	0.546			
N stage >0	0.919			
Latest treatment for CBS				
Chemotherapy alone	0.648			
Radiotherapy alone	0.406			
Concurrent chemoradiotherapy	0.007	2.284 (1.259–4.143)		
Neck dissection	0.069			
Clinical follow-up	0.302			
Neck condition from CBS diagnosed backward for 6 months				
Wound infection	0.847			
Fistula formation	0.178			
Tissue necrosis	0.936			
Vessel exposure	0.993			
Treatment for CBS-related massive bleeding				
None	0.362			
Stent insertion	0.617			
Embolization	0.053			
Stent insertion and embolization	0.747			
Surgical ligation	0.178			
Local recurrence from CBS diagnosed backward for 6 months	0.022	1.976 (1.101–3.548)		
Serum marker at CBS diagnosis				
White blood count >10.0×10^3 (cells/μl)	0.885			
Monocytes >1000 (cells/μl)	0.965			
Hemoglobin <11.0 (g/dl)	0.066			
PLT >400×10^3(cells/μl)	0.091			
Albumin <3.5 (g/dl)	0.038	2.049 (1.041–4.032)	0.013	3.084 (1.267–7.510)
Corrective Ca >10.5 (mg/dl)	0.432			
LDH >250 U/l	0.050	2.186 (1.002–4.772)		
ALK-p > 100 U/l	0.781			
CRP >5 (mg/dl)	0.304			

[a]The factors with $P < 0.05$ in univariate analysis were enrolled into the forward stepwise multivariate Cox hazard regression.

recurrence were important in univariate analysis for CBS-related death. Kaplan–Meier plots revealed that these factors were useful prognostic factors (Fig. 3).

DISCUSSION

In our study, best supportive care and hypoalbuminemia were independent factors in the prediction of prognosis for CBS-related massive bleeding and CBS-related death, respectively. These data may be helpful for clinicians to predict the risk of massive bleeding and provide improved supportive care for these patients. Other factors such as monocytosis, elevated LDH and local recurrence were important for CBS-related prognosis.

Many factors predispose patients to CBS. These include radiation therapy, radical resection, flap necrosis with carotid exposure, wound infection, pharyngocutaneous fistula and recurrent tumor (1). In Taiwan, because of the unique habit of betel quid chewing, the incidence of HNC patients increases, and patients with this habit have a greater tendency towards tumour recurrence and poor outcome than those who do not chew betel quid (11–13). As the characteristics of patients in Taiwan are different from those in the Western population (12), HNC patients in Taiwan show poor treatment response and greater complications than those in the Western countries (13). This also confers more risk of CBS.

Age, performance status and TNM stage were considered important prognostic factors for HNC since the last decade (14). Anemia was proved to be a powerful prognostic factor (15), because of its relationship to tumour hypoxia. Tumour hypoxia is linked to poor tumour response to radiotherapy, aggressive tumour phenotype and poor outcome following surgery (16). Hematologic factors, such as monocytosis, thrombocytopenia and elevated LDH are also reported to be important prognostic factors (9,10). In this study, we showed that CBS-related prognostic factors were similar to prognostic factors for HNC. These data are compatible with our concept that CBS is associated with cancer.

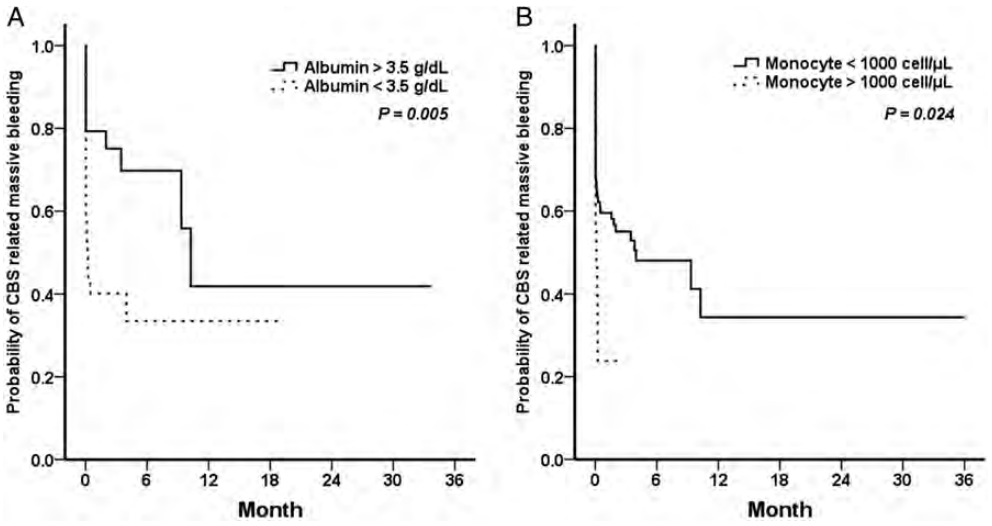

Figure 2. Prognostic factors for CBS-related massive bleeding. Kaplan–Meier plots revealed that (a) hypoalbuminemia ($P = 0.005$) and (b) monocytosis ($P = 0.024$) could effectively predict massive bleeding.

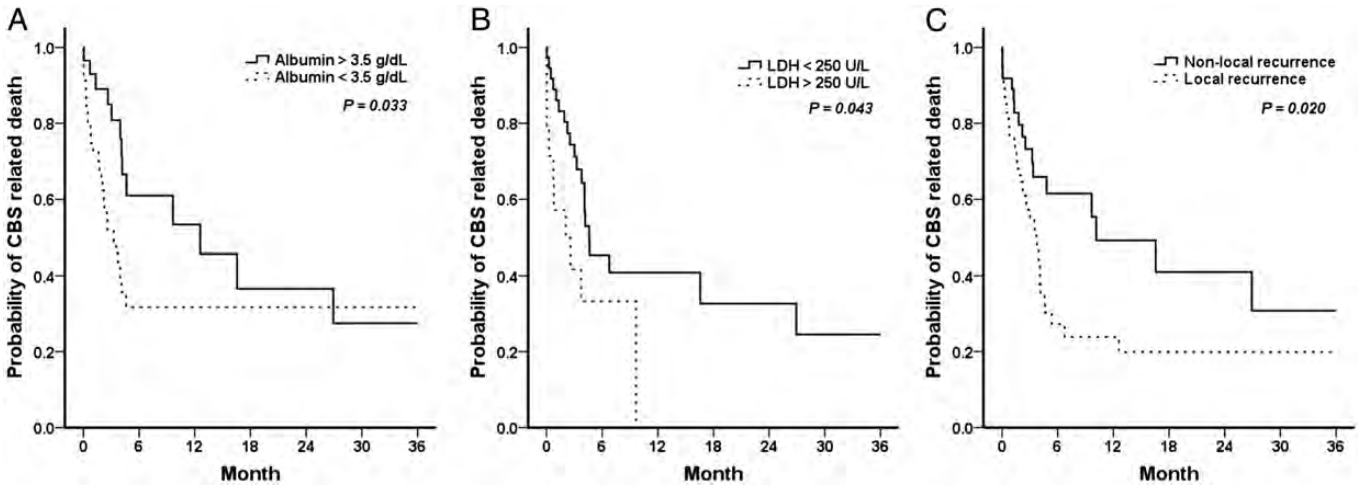

Figure 3. Prognostic factors for CBS-related death. Kaplan–Meier plots revealed hypoalbuminemia, elevated LDH and local recurrence were useful prognostic factors for CBS-related death (a–c; $P = 0.033$, 0.043 and 0.020, respectively).

In the current study, serum albumin was the most important prognostic factor for CBS. It was previously shown that serum albumin played a major role in prognosis for solid tumours (17,18). For HNC patients, hypoalbuminemia was recognized as an independent prognostic factor (19–21). Hypoalbuminemia was also considered an important prognostic factor for outcomes, such as larynx preservation and postoperative wound infection (22,23). The possible reasons for hypoalbuminemia being a significantly poor prognostic factor for CBS patients may be the poor nutrition status and the presence of systemic inflammatory response (24,25). Besides, poor nutrition leads to less soft-tissue coverage, resulting in development of weak arterial walls in the neck area.

The presence of an inflammatory response is also associated with hypoalbuminemia (7). Intravascular wound healing is related to the inflammatory response, and monocytes/macrophages played important roles (4). For patients with malignant tumours, hypoalbuminemia is explained by the presence of an ongoing inflammation-like response that contributes to the progressive loss of vital protein components from the body (26). Because local inflammatory responses were linked to intravascular wound healing (4), this hypothesis may be compatible with the importance of monocytosis on CBS-related massive bleeding in our study. The significantly negative correlation between serum albumin and CRP level also confirmed our hypothesis (Supplementary data, Fig.).

In consideration of the treatment for CBS-related massive bleeding and death, some prophylactic methods were published that were effective in decreasing massive bleeding, such as endovascular interventions and surgical clipping (27,28). Meyers et al. (29) suggested that embolization can be effective management for patients with higher risk of hemorrhage and is associated with a reduction in procedural morbidity and mortality. The role of endovascular stent implantation

is to restore cerebral blow flow. For pathologic vessel wall, embolization is useful to prevent rupture by protecting the susceptible wall from the stress of pulsatile blood (30).

In conclusion, best supportive care and serum albumin are the most important prognostic factors of CBS. Our results may help clinicians provide better supportive care for CBS patients, especially to prevent the event of massive bleeding.

Authors' contributions

H.J.L. carried out the data collection, analysis and manuscript preparation. K.-W.C., M.-H. C., P.-Y.C., S.K.T., C.-H. T., P.M.-H.C. and M.H.Y. contributed to study design and data acquisition. P.M.-H.C. and M.-H.Y. participated in the study design, critically appraised the manuscript and revised the manuscript. All the authors read and approved the final manuscript.

Supplementary data

Supplementary data are available at http://www.jjco.oxfordjournals.org.

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Conflict of interest statement

None declared.

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