This is a peer-reviewed, accepted author manuscript of the following research article: Crawford, J. E., Zubair, F., Baniulyte, G., Wales, C. J., Ansell, M., Thomson, E., Hislop, S., MacIver, C., Devine, J., McCaul, J., Young, D., & McMahon, J. (2020). Postoperative delirium in patients with head and neck oral cancer in the West of Scotland. *British Journal of Oral and Maxillofacial Surgery*. https://doi.org/10.1016/j.bjoms.2020.08.116

Post-Operative Delirium in patients with Head and Neck Oral Cancer in the West of Scotland

James Edwin Crawford*[1]
Farhan Zubair[2]
Gabriele Baniulyte[3]
Craig Wales[4]
Mark Ansell[5]
Ewen Thompson[6]
Stuart Hislop[7]
Colin MacIver[8]
John Devine[9]
Jim McCaul[10]
David Young[11]
Jeremy McMahon[12]

1. Clinical Fellow in Maxillofacial Surgery. Oral and Maxillofacial Surgery Department, Institute of Neurological Sciences, Queen Elizabeth University Hospital, Govan Road, Glasgow, G51 4TF. Jamescrawford1@nhs.net
2. University of Glasgow Medical Student. farhan123zubair@gmail.com
3. Dental Core Trainee in Maxillofacial Surgery. Oral and Maxillofacial Surgery Department, Institute of Neurological Sciences, Queen Elizabeth University Hospital, Govan Road, Glasgow, G51 4TF. gabriele.baniulyte@nhs.net
4. Consultant Oral and Maxillofacial Surgeon. Oral and Maxillofacial Surgery Department, Institute of Neurological Sciences, Queen Elizabeth University Hospital, Govan Road, Glasgow, G51 4TF. craig.wales@nhs.net
5. Consultant Oral and Maxillofacial Surgeon. Oral and Maxillofacial Surgery Department, Institute of Neurological Sciences, Queen Elizabeth University Hospital, Govan Road, Glasgow, G51 4TF. mansell@nhs.net
6. Consultant Oral and Maxillofacial Surgeon. Oral and Maxillofacial Forth Valley Royal Hospital, Stirling Road, Larbert, FK5 4WR. Ewen.thomson@fvah.scot.nhs.uk
7. Consultant Oral and Maxillofacial Surgeon. Oral and Maxillofacial Surgery Department, Kilmarnock Road, Crosshouse, Kilmarnock KA2 0BE. stuart.hislop@aaaht.scot.nhs.uk
8. Consultant Oral and Maxillofacial Surgeon. Oral and Maxillofacial Surgery Department, Institute of Neurological Sciences, Queen Elizabeth University Hospital, Govan Road, Glasgow, G51 4TF. colinmaciver@nhs.net
9. Consultant Oral and Maxillofacial Surgeon. Oral and Maxillofacial Surgery Department, Institute of Neurological Sciences, Queen Elizabeth University Hospital, Govan Road, Glasgow, G51 4TF
10. Consultant Oral and Maxillofacial Surgeon. Oral and Maxillofacial Surgery Department, Institute of Neurological Sciences, Queen Elizabeth University Hospital, Govan Road, Glasgow, G51 4TF. Jim.mccaul@mac.com
11. Senior Lecturer in Mathematics and Statistics, University of Strathclyde, Livingstone Tower,16 Richmond St, Glasgow G1 1XQ. david.young@strath.ac.uk

12. Consultant Oral and Maxillofacial Surgeon. Oral and Maxillofacial Surgery Department, Institute of Neurological Sciences, Queen Elizabeth University Hospital, Govan Road, Glasgow, G51 4TF. jeremymcmahon@nhs.net

Corresponding Author
James E Crawford BDS MFDS (RCPS Glas) MBChB PG Cert Med Ed.
Clinical Fellow in Oral and Maxillofacial Surgery. Oral and Maxillofacial Surgery Department, Institute of Neurological Sciences, Queen Elizabeth University Hospital, Govan Road, Glasgow, G51 4TF. Scotland. United Kingdom.
Jamescrawford1@nhs.net

Article Word Count: 3171

This is a peer-reviewed, accepted author manuscript of the following research article: Crawford, J. E., Zubair, F., Baniulyte, G., Wales, C. J., Ansell, M., Thomson, E., Hislop, S., MacIver, C., Devine, J., McCaul, J., Young, D., & McMahon, J. (2020). Postoperative delirium in patients with head and neck oral cancer in the West of Scotland. *British Journal of Oral and Maxillofacial Surgery*. https://doi.org/10.1016/j.bjoms.2020.08.116

Abstract

Aims

To determine the prevalence and association of post-operative delirium (POD) in Head and Neck (H&N) cancer patients undergoing free flap reconstruction at the QEUH OMFS unit. To assess whether these determinants can be modified to optimise patient care and reduce the occurrence of POD.

Introduction

Delirium remains an important problem in the postoperative care of patients undergoing major H&N surgery. Early detection and management improves overall patient outcomes.

Methods

Patient database containing details of pre-operative physical status including alcohol misuse, chronic co-morbidity, and physiological status of 1006 patients that underwent major H&N surgery with free flap repair at the QEUH from 2009-2019. Factors associated with delirium were studied, identifying univariate associations as well as multivariate modelling to determine independent risk factors.

Results

Incidence of POD within the cohort was 7.5% (75/1006).

- 53 male: 22 female
- average age 65.41 years

The development of POD was strongly associated with pre-existing medical comorbidities, excess alcohol and smoking.
Prolonged surgical operating time (>700 minutes), tracheostomy, blood transfusion and bony free-flaps were associated with POD.
Those with POD were at an increased risk of post-operative wound and lung complications.
Individuals with POD were more likely to require hospital in excess of 21 days.

Conclusion

Diagnosis and detection of delirium in post-operative H&N oncology patients is difficult. Pre-surgical assessment should identify risk factors for developing delirium. Optimising the diagnosis and treatment of delirium will enhance patient care, by reducing further medical and surgical complications and reducing overall hospital stay.

Abstract Word Count: 246

Keywords: Head and Neck; Delirium; Free Flap; ERAS; Oral Cancer; Risk Factors; Post-Operative Care

This is a peer-reviewed, accepted author manuscript of the following research article:
Crawford, J. E., Zubair, F., Baniulyte, G., Wales, C. J., Ansell, M., Thomson, E., Hislop, S., MacIver, C., Devine, J., McCaul, J., Young, D., & McMahon, J. (2020). Postoperative delirium in patients with head and neck oral cancer in the West of Scotland. *British Journal of Oral and Maxillofacial Surgery*. https://doi.org/10.1016/j.bjoms.2020.08.116

Abbreviations:

- POD: Post-operative delirium
- ACE -27: Adult Comorbidity Evaluation 27
- ERAS – Enhanced Recovery After Surgery
- 4AT: The 4As Test
- DTS-bCAM: Delirium Triage Score – brief Confusion Assessment Method
- NuDESC: Nursing Delirium Screening Checklist

This is a peer-reviewed, accepted author manuscript of the following research article: Crawford, J. E., Zubair, F., Baniulyte, G., Wales, C. J., Ansell, M., Thomson, E., Hislop, S., MacIver, C., Devine, J., McCaul, J., Young, D., & McMahon, J. (2020). Postoperative delirium in patients with head and neck oral cancer in the West of Scotland. *British Journal of Oral and Maxillofacial Surgery*. https://doi.org/10.1016/j.bjoms.2020.08.116

Introduction

Delirium also known as an 'acute confusional state' is a common clinical syndrome characterised by disturbed consciousness, cognitive function or perception, which has an acute onset and fluctuating course[1]. It can develop over days to weeks and is a serious condition that is associated with poor outcomes. Fortunately, it can be prevented and treated if identified early and managed urgently.
Delirium is subclassified into three types[2]:

- Hyperactive delirium (20% prevalence)
- Hypoactive delirium (50% prevalence)
- Mixed type - combination of hyperactive and hypoactive delirium (30% prevalence)

The aetiology of delirium is multifactorial but can be found to arise as a consequence to changes in the patient's physiological status. The causes of hyperactive and hypoactive delirium are the same. Often patients may experience both types and fluctuate between them. This may be as a result of active disease, surgical insult, substance withdrawal, intoxication or exposure to toxins[2].

The diagnosis of delirium is based upon the definitions presented using the Diagnostic and Statistical Manual of Mental Disorders (DSM V) or the International Classification of Diseases 10 (ICD 10)[3, 4]. These are represented in full in ***Appendix A***.

Delirium is a common condition. It has a prevalence of 20-30% in medical based hospital inpatients and up to 50% in orthogeriatric inpatients post-operatively[5].

Specific to the maxillofacial population, Zhu et al 2017, in their systematic review of post-operative H&N cancer patients, found that the incidence of delirium varied somewhat between 11.5% and 35.11%, with an estimated overall prevalence of 19.26%[6]. More recently, Densky et al found an incidence of 10.9% in a population of 515 H&N free flap reconstruction patients[7].

The diagnosis of delirium is based upon clinical assessment of a patient, in conjunction with known risk factors. Identification of patients potentially at risk of delirium is vital in order to instigate early preventative measures and ultimately improve long term outcomes.
Post-operative delirium is associated with longer hospital stays, poorer functional recovery, and higher healthcare costs[1,3,8].

Delirium assessment tools are recommended within the clinical setting to formally diagnose delirium. NICE recommend the use of the short Confusion Assessment Method (CAM). However, this requires pre-requisite training to increase the operator validity and accuracy of clinical assessment. A recent systematic review of delirium assessment tools highlights the need for a "simple" bedside assessment of delirium and recommends the use of[9]:

- The 4As Test (4AT)
- Delirium Triage Score – brief Confusion Assessment Method (DTS-bCAM)
- Nursing Delirium Screening Checklist (NuDESC)

This is a peer-reviewed, accepted author manuscript of the following research article:
Crawford, J. E., Zubair, F., Baniulyte, G., Wales, C. J., Ansell, M., Thomson, E., Hislop, S., MacIver, C., Devine, J., McCaul, J., Young, D., & McMahon, J. (2020). Postoperative delirium in patients with head and neck oral cancer in the West of Scotland. *British Journal of Oral and Maxillofacial Surgery*. https://doi.org/10.1016/j.bjoms.2020.08.116

The 4AT has become the more widely adopted and clinically useful bedside clinical delirium assessment tools (***APPENDIX B***) [10-12]. It is based upon the 5 elements of the DSM V classification. It has a sensitivity and specificity of 89.7% and 84.1% respectively. The 4AT is easy to implement and simple to master and incorporate into the general assessment of a patient in a ward-based setting [12].

Zhu et al identified multiple risk factors associated with the development of delirium in those undergoing major H&N surgery[6]:

- Age > 70 years
- Male Sex
- Hypertension
- Surgical duration
- Blood Transfusion
- ASA> III
- Neck Dissection
- Tracheostomy
- Free Flap Reconstruction
- Neck Dissection
- Tracheostomy
- Free Flap Reconstruction

They concluded that these contribute to the pathogenesis and development of delirium within the operated H&N cancer population[6].

Consequently, it is clear that delirium plays an important role in the post-operative care, management and recovery of those undergoing complex H&N cancer operations.

This is a peer-reviewed, accepted author manuscript of the following research article: Crawford, J. E., Zubair, F., Baniulyte, G., Wales, C. J., Ansell, M., Thomson, E., Hislop, S., MacIver, C., Devine, J., McCaul, J., Young, D., & McMahon, J. (2020). Postoperative delirium in patients with head and neck oral cancer in the West of Scotland. *British Journal of Oral and Maxillofacial Surgery*. https://doi.org/10.1016/j.bjoms.2020.08.116

Material and Methods

A patient database containing details and complications of all the patients undergoing microvascular free-flap reconstruction for H&N cancer was retrospectively analysed. This database collectively contained detailed information for 1006 patients treated at the Queen Elizabeth University Hospital Glasgow (formally the Southern General Hospital Glasgow) over a 10-year period (January 2009 – December 2019).
Post – operative delirium was highlighted as being present by searching the database for terms: “delirium”, “acute confusional state” and “confusion”.

This database was formulated on a continually updated MS Excel file. Patient details were anonymised and transferred to IBM SPSS Version 25 (2019) for statistical analysis. Data entries were “cleaned” for erroneous inputs prior to statistical analysis.

Statistical analyses

Post-operative complications including delirium were identified and individually coded to allow comparisons. Factors associated with delirium were studied, identifying univariate associations as well as multivariate modelling to determine independent risk factors.
P values of < 0.05 were counted as significant.
All statistical analyses were conducted by the authors.

Results

General Demographics and Pre-Operative Physiological Status

The Database consisted of 1006 patient records from January 2009 – December 2019 (n=1006).
75/ 1006 (7.5%) of patients were identified as having post-operative delirium (POD). Of these, 53 (71%) were male and 22 (29%) female, giving a 2.4: 1 (m: f) ratio.

Male patients were more likely to develop POD in comparison to females (OR 1.58; 95% CI 0.94-2.66; P<0.08).

Patients greater than 65.41(P<0.05). years of were found to be of greater risk in developing POD. Those over 65 years had an OR of 1.5 (95% CI 0.96-2.47; p=0.071) of developing POD.

Patients who smoked tobacco (>20 cigarettes per day) were found to be at increased risk of POD (OR 1.69; 95% CI 1.04 - 2.7; P<0.05).

Alcohol consumption (>21 units per week-prior to recent change of 14) was associated with a greater risk of developing POD (OR 1.75; 95% CI 1.02 – 23.0; P<0.05).

Those with known co-morbidities specifically vascular disease (OR 2.0; 95% CI 1.1 – 3.3; P< 0.05) and COPD (OR 2.23; 95% CI 1.2 – 4.3; P<0.05) were at increased risk of POD. Vascular disease constituted those with ischaemic heart disease; cerebral vascular disease and/ or peripheral vascular disease.

There was no correlation noted for those with diabetes (OR 0.87; 95% CI 0.34 - 2.2; P < 0.78), however only 5 patients out of 75 had diabetes within this cohort.

Using formal pre-assessment risk stratification scales demonstrated a clear associated link to the risk of POD Adult Comorbidity Evaluation 27 (ACE 27 score) (***Appendix C***)[13, 14].

The use of ACE-27 demonstrated that the more co-morbidities an individual had prior to any surgical intervention, dramatically increased their risk of developing POD (***Figure 1)***.

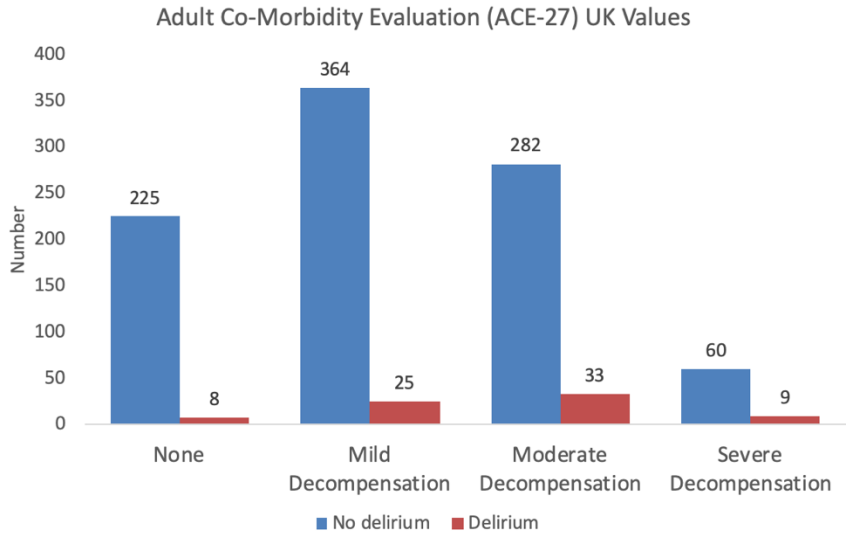

Figure 1| ACE-27 and the association with Post-Operative Delirium

Peri-operative status and Surgical activity

All patients within the cohort had a microvascular free flap reconstruction.

Operating times greater than 644 minutes increased the risk of delirium (P<0.05). Mean difference of 61 minutes (95% CI 55 - 172; P<0.05):

- Mean duration in those with POD - 703 minutes
- Mean duration in those without POD – 644 minutes

Patients undergoing operations lasting greater than 703 minutes (11 hours 43 minutes) have an OR of 1.9 of developing POD.

68/75 (91%) of patients with delirium had a tracheostomy. 805/931(86.5%) of the patients without delirium had a tracheostomy. The OR of developing delirium with a tracheostomy was 1.33 (P =0.515; 95% CI 0.56-3.16). This was not statistically significant, as the majority of patients operated upon had a tracheostomy.

34/75 (45%) patients with POD underwent a blood transfusion (≥2 units) in comparison to 300/931 (32%) without POD. Those who required a blood transfusion perioperatively had an OR of 1.744; 95% CI 1.085-2.805 (p<0.05).

The type of flap used in reconstructive surgery was found to be of importance. Those undergoing a bony composite flap had an OR of 1.6 (CI 1-2.6; P<0.05) in comparison to a full soft tissue free-flap.

This is a peer-reviewed, accepted author manuscript of the following research article: Crawford, J. E., Zubair, F., Baniulyte, G., Wales, C. J., Ansell, M., Thomson, E., Hislop, S., MacIver, C., Devine, J., McCaul, J., Young, D., & McMahon, J. (2020). Postoperative delirium in patients with head and neck oral cancer in the West of Scotland. *British Journal of Oral and Maxillofacial Surgery*. https://doi.org/10.1016/j.bjoms.2020.08.116

Post-operative period

Patients who developed POD had a greater risk of developing post-operative wound complications (OR 1.6; 95% CI 1.0 – 2.7; P<0.05) and pulmonary complications (OR 3.6; 95% CI 2.5 – 6.5; 95%; P<0.05).
Wound complications included infected haematoma; flap failure or haemorrhage.
Pulmonary complications included chest infections or tracheostomy issues.

H&N patients with POD had a longer duration hospital stay in comparison to those who did not develop POD (32 days in comparison to 21 days respectively). The mean difference was 11 days (P<0.05; 95% CI = 7-15 days). Those with POD had an OR of 3 (95% CI 1.9-5.2) for a prolonged hospital stay lasting > 21 days.

20/75 (27%) of patients with POD required a return to theatre which was identical to those without POD 248/931 (27%). OR = 1; P = 0.996 therefore this was not significant.

A full and detailed summary table of the complete pre, peri and post-operative data analyses is demonstrated in ***Table 1***. The principle outcomes of this data are visualised graphically using the Odds Ratio (OR) in ***Figure 2***.

This is a peer-reviewed, accepted author manuscript of the following research article:
Crawford, J. E., Zubair, F., Baniulyte, G., Wales, C. J., Ansell, M., Thomson, E., Hislop, S., MacIver, C., Devine, J., McCaul, J., Young, D., & McMahon, J. (2020). Postoperative delirium in patients with head and neck oral cancer in the West of Scotland. *British Journal of Oral and Maxillofacial Surgery*. https://doi.org/10.1016/j.bjoms.2020.08.116

Pre-Operative Data Analysis Summary				
Parameter	**Statistical technique**	**Result (Odds Ratio or mean)**	**95% Confidence Interval (95% CI) or Standard Deviation (SD)**	**P Value**
Post-Operative Delirium (POD)	Incidence	75/1006 x 100% = **7.5%**	N/A	N/A
Gender (male)	Binary Logistical regression – Odds ratio	OR **1.582** • POD Male 53/ 75 (**71%**) • POD Female 22/75 (**29%**) • No POD Male 615/931 (**66%**) • No POD female 391/931 (**34%**)	95% CI: 0.946 – 2.645	P < 0.08
Age	Comparison of means (Independent sample T Test)	Delirium – **65.4**1 years No Delirium – **61.15** years	SD - 13.16 years SD - 11.1 years	P <0.05 P <0.05
Age	Binary Logistical regression – Odds ratio	Age > 65 years **OR 1.5**	95% CI 0.96-2.47	P=0.071
Smoking (Current)	Binary Logistical regression – Odds ratio	OR **1.69** • POD smoker 40/75 **(53%)** • POD Non-smoker **(47%)** • No POD smoker 376/931 **(40%)** • No POD Non-smoker 555/931 **(60%)**	95% CI: 1.04 - 2.7	P<0.034
Alcohol Excess	Binary Logistical regression – Odds ratio	OR **1.658** • POD alcohol 55/75 **(73%)** • POD No alcohol **(27%)** • No POD alcohol 577/931 **(62%)** • No POD No alcohol 354/931 **(38%)**	95% CI: 0.977-2.814	P<0.061
Vascular Disease	Binary Logistical regression – Odds ratio	OR **1.950** • POD vascular disease 20/75 **(27%)** • POD No vascular disease 55/75 **(73%)** • No POD vascular disease 149/931 **(16%)** • No POD No vascular disease 782/931 **(84%)**	95% CI 1.133-3.358	P< 0.016
COPD	Binary Logistical regression – Odds ratio	OR **2.226** • POD COPD 15/75 **(20%)** • POD No COPD 60/75 **(80%)** • No POD COPD 94/931 **(10%)** • No POD No COPD 837/931 **(90%)**	95% CI 1.216-4.075	P<0.009
Diabetes	Binary Logistical regression – Odds ratio	OR **0.901** • POD Diabetes 5/75 **(7%)** • POD No Diabetes 70/75 **(93%)** • No POD Diabetes 71/931 **(8%)** • No POD No Diabetes 860/931 **(92%)**	95% CI 0.352-2.308	P <0.828
ACE-27 score	Binary Logistical regression – Odds ratio	None OR **1 (REFERENCE)** • (Mild) OR **2.159** • (moderate) OR **3.678** • (Severe) OR **4.714**	N/A 95% CI 0.918-5.074 95% CI 1.597-8.472 95% CI 1.686-13/181	N/A P =0.078 P =0.002 P =0.003
Peri-operative data analysis Summary				
Parameter	**Statistical technique**	**Result (Odds Ratio or mean)**	**95% Confidence Interval (95% CI) or Standard Deviation (SD)**	**P Value**
Tracheostomy	Binary Logistical regression – Odds ratio	**OR 1.520** • POD Trache **68**/75 **(91%)** • POD No Trache 7/75 **(9%)** • No POD Trache 805/931 **(86%)** No POD No Trache 126/931 **(14%)**	95% CI 0.683-3.385	P = 0.305
Free flap anatomy	Binary Logistical regression – Odds ratio	Soft tissue flap **OR 1 (REFERENCE)** • POD 45/75 (60%) • No POD 660/931 (71%) Composite flap **OR 1.624** • POD 30/75 (40%) No POD 271/931 (29%)	N/A 95% CI 1.002-2.632	N/A P = 0.049
Blood Transfusion	Binary Logistical regression – Odds ratio	**OR 1.744** • POD transfusion 34/75 **(45%)** • POD No transfusion 41/75 **(55%)** • No POD transfusion 300/931 **(32%)** No POD No transfusion 631/931 **(68%)**	95% CI 1.085-2.805	P=0.022
Surgical duration	Comparison of means (Independent sample T Test)	Mean duration in those with delirium – **703 minutes** Mean duration in those without delirium – **644 minutes**	SD - 171 minutes SD - 160 minutes	P<0.05 P<0.05
Surgical duration	Binary Logistical regression – Odds ratio	Theatre duration >700 minutes **OR 1.9**	95% CI 1.1-3.1	P=0.013
Post-Operative Data Analysis Summary				
Parameter	**Statistical technique**	**Result (Odds Ratio or mean)**	**95% Confidence Interval (95% CI) or Standard Deviation (SD)**	**P Value**
Wound complications	Binary Logistical regression – Odds ratio	**OR 1.733** • POD Wound Comp 45/75 **(60%)** • POD No Wound Comp 30/75 **(40%)** • No POD Wound Comp 432/931 **(46%)** No POD No Wound Comp 499/931 **(54%)**	95% CI 1.073-2.799	P=0.025
Pulmonary complications	Binary Logistical regression – Odds ratio	**OR 4.065** • POD Pulm Comp 42/75 **(56%)** • POD No Pulm Comp 33/75 **(44%)** • No POD Pulm Comp 222/931 **(24%)** • No POD No Pulm Comp 709/931 **(76%)**	95% CI 2.515-6.570	P<0.001
Hospital stay	Comparison of means (Independent sample T Test)	POD hospital stay duration: **32 days** No POD hospital stay duration: **21 days**	22 days 14 days	P<0.05 P<0.05
Hospital Stay	Binary Logistical regression – Odds ratio	Stay > 21 days **OR 3.098**	95% CI 1.857-5.168	P<0.001
Return to theatre	Binary Logistical regression – Odds ratio	**OR 1.001** • POD return 20/75 **(27%)** • POD No return 55/75 **(73%)** • No POD return 248/931 **(27%)** No POD No return 683/931 **(73%)**	95% CI 0.588-1.705	P<0.996

Table 1| Summary of statistical analysis for pre, peri and post-operative parameters with relevance to the development of post-operative delirium (POD).

This is a peer-reviewed, accepted author manuscript of the following research article:
Crawford, J. E., Zubair, F., Baniulyte, G., Wales, C. J., Ansell, M., Thomson, E., Hislop, S., MacIver, C., Devine, J., McCaul, J., Young, D., & McMahon, J. (2020). Postoperative delirium in patients with head and neck oral cancer in the West of Scotland. *British Journal of Oral and Maxillofacial Surgery*. https://doi.org/10.1016/j.bjoms.2020.08.116

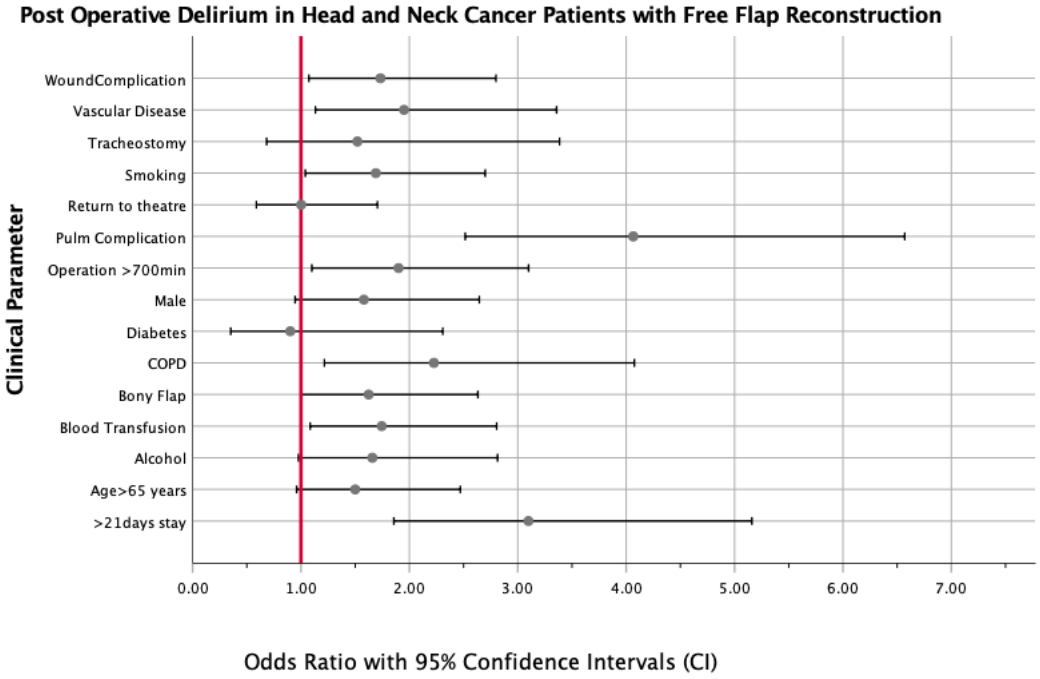

Figure 2| Post-Operative Delirium in Head and Neck Cancer Patients with Free Flap Reconstruction in the West Coast of Scotland. Odds Ratio (OR) with 95% Confidence Intervals (CI). Red line | represents an Odds ratio of 1.0.

This is a peer-reviewed, accepted author manuscript of the following research article: Crawford, J. E., Zubair, F., Baniulyte, G., Wales, C. J., Ansell, M., Thomson, E., Hislop, S., MacIver, C., Devine, J., McCaul, J., Young, D., & McMahon, J. (2020). Postoperative delirium in patients with head and neck oral cancer in the West of Scotland. *British Journal of Oral and Maxillofacial Surgery*. https://doi.org/10.1016/j.bjoms.2020.08.116

Biochemical Parameters

No significant clinical correlation was detected for pre or post-operative haemoglobin; White Cell Count (WCC); C-Reactive Protein (CRP) or albumin levels in relation to the development of POD (***Table 2***).

There was a statistically significant difference in the pre-operative haemoglobin (Hb) levels in those with POD and those without. Counterintuitively, a higher Hb was associated with POD, by the small magnitude of 5.38g/L. This represents the relatively small number of patients with delirium within this cohort (75/1006). Such a small differential in Hb levels would not be clinically significant and could represent differences in patient hydration status.

There was a small statistically significant difference noted in the 72-hour albumin Nadir between those with and without delirium, however this was in the magnitude of a 1.36 difference and would not be clinically significant.

Group Statistics	**Delirium**	**Mean**	**Std. Deviation**	**Std. Error Mean**	**Mean Difference**	**95% CI of difference Upper**	**95% CI of difference Lower**	**P value**
Pre – op Haemoglobin (g/L)	Delirium	137.57	17.04	2.05	5.38	-0.98	-9.78	0.017
	No delirium	132.19	18.01	0.6	-	-	-	-
Pre – op WCC ($x10^9$/L)	Delirium	8.26	2.39	0.29	0.08	0.57	-0.74	0.807
	No delirium	8.17	2.69	0.09	-	-	-	-
Pre – op Platelet ($x10^9$/L)	Delirium	283.61	89.31	10.75	-3.12	27.31	-21.07	0.8
	No delirium	286.73	99.34	3.31	-	-	-	-
Pre – op CRP (mg/L)	Delirium	14.09	19.24	2.30	-0.71	6.70	-5.28	0.816
	No delirium	14.80	24.93	0.85	-	-	-	-
Post – op CRP (72-hour peak) (mg/L)	Delirium	127.09	78.41	9.05	6.29	10.63	-23.22	0.466
	No delirium	120.80	71.28	2.35	-	-	-	-
Pre – op ALB (g/L)	Delirium	36.42	4.57	0.53	-0.73	1.85	-0.40	0.208
	No delirium	37.14	4.78	0.16	-	-	-	-
Post – op ALB (72-hour nadir) (g/L)	Delirium	22.68	5.37	0.62	-1.36	2.59	0.13	0.03
	No delirium	24.04	5.15	0.17	-	-	-	-

Table 2| Blood based analysis pre and post operatively in relation to the development of delirium.

This is a peer-reviewed, accepted author manuscript of the following research article:
Crawford, J. E., Zubair, F., Baniulyte, G., Wales, C. J., Ansell, M., Thomson, E., Hislop, S., MacIver, C., Devine, J., McCaul, J., Young, D., & McMahon, J. (2020). Postoperative delirium in patients with head and neck oral cancer in the West of Scotland. *British Journal of Oral and Maxillofacial Surgery*. https://doi.org/10.1016/j.bjoms.2020.08.116

Disease Specific Analysis

Analysing the type of disease in relation to the development of POD was particularly difficult due to the multitude of surgical sites on the H&N and the disease processes themselves. Disease sites were compiled into three categories (***Table 3***):

1) Oral cavity and Maxilla
2) Oropharynx and hypopharynx
3) Other – which included the orbit, scalp and major salivary glands

Tumour staging (T and N) were independently analysed. No recording of Metastatic disease was present within the database.

The results do not demonstrate a particular surgical site or disease stage that is associated with an increased risk of POD. The OR does increase with increased regional nodal disease; however, this was not statistically significant.

Parameter	Statistical technique	Result (Odds Ratio)	95% Confidence Interval	P Value
Tumour site	Binary Logistical regression – Odds ratio	Other OR **1 (REFERENCE)** • POD 11/75 (**15%**) • No POD 127/931 (**14%**) Oral Cavity including Maxilla **OR 0.949** • POD 59/ 75 (**79%**) • No POD 718/ 931 (**77%**) Oropharynx and hypopharynx **OR 0.671** • POD 5/75 (**7%**) • No POD 86/931(**9%**)	N/A 95% CI 0.485-1.855 95% CI 0.225-2.0	N/A P = 0.878 P = 0.474
Tumour T Classification	Binary Logistical regression – Odds ratio	Other OR **1 (REFERENCE)** • POD 17/75 (**23%**) • No POD 168/931 (**18%**) T1 **OR 0.607** • POD 7/75 (**9%**) • No POD 114/931 (**12%**) T2 **OR 0.689** • POD 15/75 (**20%**) • No POD 215/931 (**23%**) T3 **OR 0.682** • POD 6/75 (**8%**) • No POD 87/931 (**9%**) T4 **OR 0.857** • POD 30/75 (**40%**) • No POD 346/931 (**37%**)	N/A 95% CI 0.244-1.510 95% CI 0.335-1.421 95% CI 0.259-1.791 95% CI 0.460-1.597	N/A P=0.283 P=0.313 P=0.437 P=0.627
Tumour N Classification	Binary Logistical regression – Odds ratio	N0 OR **1 (REFERENCE)** • POD 48/75 (**64%**) • No POD 617/931 (**66%**) N1 **OR 1.193** • POD 9/75 (**12%**) • No POD 97/931 (**10%**) N2a **OR 1.353** • POD 4/75 (**5%**) • No POD 38/931 (**4%**) N2b **OR 1.037** • POD 10/75 (**13%**) • No POD 124/931 (**13%**) N2c **OR 1.071** • POD 3/75 (**4%**) • No POD 36/931 (**4%**) N3 **OR 0.677** • POD 1/75 (**1%**) • No POD 19/931 (**2%**)	N/A 95% CI 0.567-2.508 95% CI 0.464-3.950 95% CI 511-2.104 95% CI 0.318-3.606 95% CI 0.089-5.163	N/A P=0.642 P=0.580 P=0.921 P=0.912 P=0.706

Table 3| Disease specific parameters in relation to Post-operative Delirium in Head and Neck Cancer Patients.

This is a peer-reviewed, accepted author manuscript of the following research article:
Crawford, J. E., Zubair, F., Baniulyte, G., Wales, C. J., Ansell, M., Thomson, E., Hislop, S., MacIver, C., Devine, J., McCaul, J., Young, D., & McMahon, J. (2020). Postoperative delirium in patients with head and neck oral cancer in the West of Scotland. *British Journal of Oral and Maxillofacial Surgery*. https://doi.org/10.1016/j.bjoms.2020.08.116

Multivariate analysis

A multivariate logistical regression model was conducted using the significant variables from the univariate analyses. The final multivariate model consisted of *pulmonary complications* OR 3.221; 95% CI 1.896-5.471 (p<0.001); *hospital duration > 21 days* OR 1.026 95%CI 1.014-1.039 (p<0.001); *Age> 65 years* OR 1.035 95% CI 1.009-1.061 (p<0.009 and *Pre-operative Haemoglobin* OR 1.027 95% CI 1.012-1.043 (p<0.001).

An Area Under the Curve Receiver Operating Characteristics (AUC-ROC) was completed for this model (***Figure 3***).

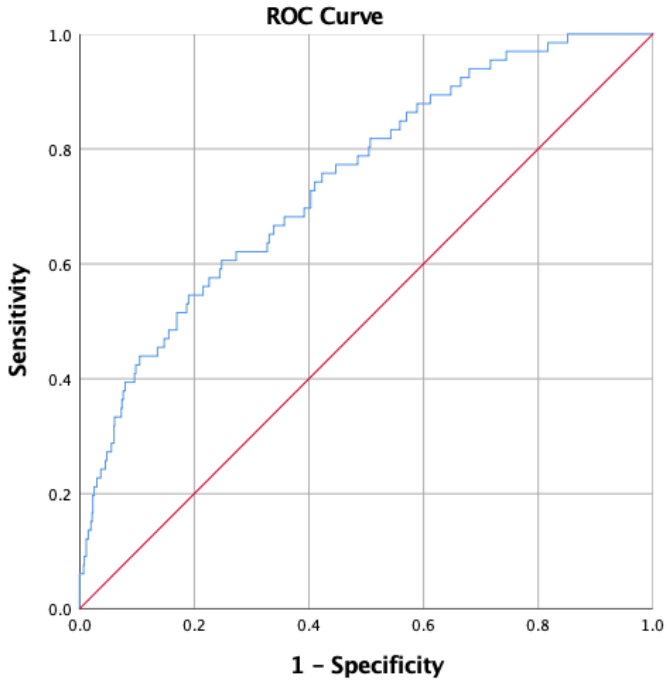

Figure 3| Area Under the Curve Receiver Operating Characteristics (AUC-ROC) analysis. This demonstrated an area under the ROC curve of 0.745 which shows a good model (the closer the area is to 1, the better the model). Sensitivity = 62.1% and specificity = 72.7% using predictive probability of <0.751 as the cut-off.

This is a peer-reviewed, accepted author manuscript of the following research article: Crawford, J. E., Zubair, F., Baniulyte, G., Wales, C. J., Ansell, M., Thomson, E., Hislop, S., MacIver, C., Devine, J., McCaul, J., Young, D., & McMahon, J. (2020). Postoperative delirium in patients with head and neck oral cancer in the West of Scotland. *British Journal of Oral and Maxillofacial Surgery*. https://doi.org/10.1016/j.bjoms.2020.08.116

Discussion

Delirium is common in post-operative H&N surgical cancer patients undergoing free flap surgery. Our study demonstrates an overall prevalence of 7.5%. This number is presumed to be an underestimate of the true reflection of this condition, due to the inherent difficulties in diagnosing and detecting delirium. Zhu et al quoted their estimated incidence at 19.26% [6]. A recent study by Densky et al in a population cohort similar to this paper, revealed an incidence of 10.9% overall in a population of 515 patients[7].

The causes of delirium are multifactorial in nature resulting in the manifestation of this condition[2]. The risk factors underpinning the aetiology of POD can be categorised into two ways:

1. Those linked to patient (Predisposing factors)
2. Those that induce delirium (Precipitating factors)

The overall POD risk results from a complex interplay between these two elements [15].

This study has demonstrated that male gender, age greater than 65 years, smoking, alcohol, vascular disease, COPD, prolonged surgical time, ACE -27 score >2, bony surgical flap reconstruction and blood transfusions increase the risk of developing post-operative delirium (POD).

Premorbid status highlighted that vascular disease increased the risk of POD. This is in keeping with other studies that demonstrate similar effects with regards to microvascular changes that exist within the cerebrovascular system and put an individual at heighted risk of post-operative neurological states of disruption [16, 17].

One of the most significant features of this study was that of COPD being markedly associated with POD. Additionally, post-operative pulmonary complications in those with POD was significantly high (OR 4.065; 95% CI 2.515-6.570) in those with POD.

These findings may be explained by long operating times and tracheostomy use. Globally this leads to impaired cerebral brain perfusion throughout prolonged operations and recovery [18]. A combination of multiorgan failure, inflammatory cytokines, microvascular damage, thrombosis and impaired oxygen metabolism may all contribute the global reduction in cerebral perfusion [18]. This was also associated in those with prolonged ITU ventilation [18]. The global reduction in cerebral perfusion may be a contributing factor to the development of POD.

The greater the number of medical co-morbidities, the greater the risk of developing POD. This has been demonstrated in other surgical specialities with similar effect [19]. The use of ACE – 27 scoring has demonstrated this clearly in our data. Many of these co-morbidities are inherent within our patient population basis and modifying these prior to surgery is not always possible. However, the ACE 27 assessment tool is a useful adjunct in assessing a patients overall physical health performance within this cohort. The premorbid risk factors and the associated comorbidities linked to the development of POD are inherently associated with the development of H&N cancer – the “common risk factors” [20].

Prolonged operating times has been previously documented as a risk for developing POD in H&N cancer surgery and our data reflects this [7,21,22]. Operations of greater than 700

minutes were associated with an increased risk of POD (OR 1.9 95% CI 1.1-3.1). Other studies range from 360-600 minutes [7,21,22]. Complex and time sensitive surgical interventions such as composite bony reconstructions are also associated with an increased risk of POD (OR of 1.6; CI 1-2.6; P<0.05). This combined with the microvascular compromises previously discussed, potentiates an individual for the development of POD and indeed surgical flap failure.
Densky et al proposed that such complex surgical operations should be performed in a tertiary unit with two surgical teams working in parallel to optimise operating times [7]. This is a technique that has been utilised within our unit throughout the duration of this study.

We found no statistically significant association between the location or extent of disease and the development of POD. However, it was noted that with increasing nodal spread, there was an increase OR. Densky et al found a similar relationship that was statistically significant [7].

Additionally, we have shown that those who develop POD have a prolonged hospital stay and are at greater risk of both surgical wound and respiratory based complications. This is due in part to the prolonged admission to hospital where upon patients are susceptible to further nosocomial infections and complications. Additionally, the altered behaviour of patients (in both the hyperactive and hypoactive delirious states) can compromise the integrity and care of wound sites and care management [23].

Identifying high risk patients with risk factors associated with POD should be highlighted at the Multidisciplinary Meeting (MDT) discussion and pre-operative assessment process. This will allow for effective surgical planning, optimising of operating times, pre-morbid condition assessments (ACE-27) and to allow patients and families to be informed of the risks relating to delirium in the post-operative period [14]. This should not be at the expense of the patients' oncological disease progression.

Assessing pre-operative risk factors, optimising surgical activity and planning post-operative care constitutes the core tenants of an enhanced recovery after surgery (ERAS) programme [24]. Many of the common risk factors inherent to post-operative complications also play a role in the development of delirium [25].
Therefore, understanding these associations will assist in the process of informing patients about their surgical planning, disease trajectory and post-operative recovery [24, 25].

Increasing the general awareness of delirium in the post-operative period is essential for all staff members caring for such patients. Educational programmes relating to delirium and highlighting the use of the 4AT should be encouraged [26].

As discussed previously, delirium is a complex interplay between predisposing and precipitating factors. Prevention may be possible to some extent and optimisation of the patient's pre-operative; peri operative and post-operative care may influence the development of POD. However, it is a disease process that is currently very common, and in many cases, we must accept that some patients will be susceptible to this illness. Staff awareness and the development of a delirium friendly hospital environments should be encouraged [27].

This is a peer-reviewed, accepted author manuscript of the following research article:
Crawford, J. E., Zubair, F., Baniulyte, G., Wales, C. J., Ansell, M., Thomson, E., Hislop, S., MacIver, C., Devine, J., McCaul, J., Young, D., & McMahon, J. (2020). Postoperative delirium in patients with head and neck oral cancer in the West of Scotland. *British Journal of Oral and Maxillofacial Surgery*. https://doi.org/10.1016/j.bjoms.2020.08.116

Our data is representative of a patient population within the UK and hope that it may be contribute to the collective data already published. Recent work has mainly originated from Japan and the United States [6, 7].
We hope this data can be applicable and generalisable to others throughout the world.

Limitations

This study was a retrospective analysis of a complications database for H&N cancer patients undergoing surgical intervention with free flap reconstruction over a 10-year period. Analysing the data for the presence of delirium was challenging. There was no distinction made between post-operative delirium, alcohol or substance misuse related withdrawal/ delirium tremens or dementia related delirium. Future updates to this database will require a formal assessment tool to be used to screen and definitively diagnose POD. Ishibashi-Kanno et al, in a similar study, utilised Psychiatric medical input to ensure a formal delirium subtype diagnosis was accurately made, by two different psychiatry clinicians [28].

An additional confounding variable that was not possible to account for was the consideration of pre-existing pre-operative cognitive impairment. In those > 65 years who are admitted to hospital, delirium is prevalent in up to 50% and a high proportion of those affected (30-40%) are preventable [29]. The interface between delirium and dementia is poorly understood, however dementia is a leading risk factor for the development of delirium [30]. Future data entry must be explicit about formal cognitive impairments.

Other features not analysed in this data cohort, was the use of medications – especially benzodiazepines, opiates and anaesthetic agents. All of which are commonly instigated in the pathophysiology of the development of delirium [15].

This is a peer-reviewed, accepted author manuscript of the following research article: Crawford, J. E., Zubair, F., Baniulyte, G., Wales, C. J., Ansell, M., Thomson, E., Hislop, S., MacIver, C., Devine, J., McCaul, J., Young, D., & McMahon, J. (2020). Postoperative delirium in patients with head and neck oral cancer in the West of Scotland. *British Journal of Oral and Maxillofacial Surgery*. https://doi.org/10.1016/j.bjoms.2020.08.116

Conclusion

Delirium remains an important problem in the postoperative care of patients undergoing major H&N surgery. It impacts upon an individual's surgical journey, risk of complications, their hospital stay and the overall financial cost to the health service with prolonged admissions and wound complications.

To date this study represents the largest retrospective cohort analysis of delirium within the post-operative head and H&N free-flap patient population.

Our data is in keeping with that of international figures and highlights the importance of delirium in the post-operative care of H&N cancer patients undergoing free flap reconstructive surgery.

A small proportion (7.5%) of our patient population will experience delirium in some form. We believe that our data underestimates the total prevalence, given the inherent challenges in recognition, diagnosis and overall management of this condition.

It is clear there is a profound burden placed upon healthcare services in providing care for such individuals when they are at their most vulnerable. It is imperative therefore to emphasise the importance of delirium recognition in the post-operative period.

We believe the implementation and use of the 4AT screening tool should be utilised routinely. Engaging medical, dental, nursing and allied health professionals in the appreciation, recognition, diagnosis and management of delirium would be highly recommended and encouraged.

Ultimately, early detection, diagnosis and management of post-operative delirium within our H&N cancer surgery population will improve overall patient outcomes including:

- Reduction in overall complications
- Shorter hospital admission
- Reduced financial burden
- Reduced psychosocial impact on patients and their families

This is a peer-reviewed, accepted author manuscript of the following research article: Crawford, J. E., Zubair, F., Baniulyte, G., Wales, C. J., Ansell, M., Thomson, E., Hislop, S., MacIver, C., Devine, J., McCaul, J., Young, D., & McMahon, J. (2020). Postoperative delirium in patients with head and neck oral cancer in the West of Scotland. *British Journal of Oral and Maxillofacial Surgery*. https://doi.org/10.1016/j.bjoms.2020.08.116

References

[1] NICE Guidelines CG 103: Available online at: https://www.nice.org.uk/guidance/cg103

[2] Hosker Christian, Ward David. Hypoactive delirium. *BMJ* 2017; 357 :j2047

[3] American Psychiatric Association. Diagnostic and statistical manual of mental disorders. (fifth edition). DSM-5. Washington, DC: American Psychiatric Publishing 2013.

[4] Statistical Classification of Diseases and Related Health Problems (**ICD**). Updated 2016. Available online at:https://www.who.int/classifications/icd/en/GRNBOOK.pdf

[5] Albrecht, J. S., Marcantonio, E. R., Roffey, D. M., Orwig, D., Magaziner, J., Terrin, M., … Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair Cognitive Ancillary Study Investigators (2015). Stability of postoperative delirium psychomotor subtypes in individuals with hip fracture. *Journal of the American Geriatrics Society*, *63*(5), 970–976. doi:10.1111/jgs.13334

[6] Yun Zhu, Gangpu Wang, Shengwen Liu, Shanghui Zhou, Ying Lian, Chenping Zhang, Wenjun Yang, Risk factors for postoperative delirium in patients undergoing major head and neck cancer surgery: a meta-analysis, *Japanese Journal of Clinical Oncology*, Volume 47, Issue 6, June 2017, Pages 505–511, https://doi.org/10.1093/jjco/hyx029

[7] Densky J, Eskander A, Kang S, et al. Risk Factors Associated With Postoperative Delirium in Patients Undergoing Head and Neck Free Flap Reconstruction. *JAMA Otolaryngol Head Neck Surg.* 2019;145(3):216–221. doi:10.1001/jamaoto.2018.3820

[8] Marcantonio ER, Flacker JM, Michaels M, Resnick NM. Delirium is independently associated with poor functional recovery after hip fracture. J Am Geriatr Soc 2000;48:618–24.

[9] Jayita De, Anne P. F. Wand, Delirium Screening: A Systematic Review of Delirium Screening Tools in Hospitalized Patients, *The Gerontologist*, Volume 55, Issue 6, December 2015, Pages 1079–1099, https://doi.org/10.1093/geront/gnv100

[10] Bauernfreund Y, Butler M, Ragavan S, *et al.* TIME to think about delirium: improving detection and management on the acute medical unit. *BMJ Open Quality* 2018;**7:**e000200. doi: 10.1136/bmjoq-2017-000200

[11] Bellelli, G., Morandi, A., Davis, D. H. J., Mazzola, P., Turco, R., Gentile, S., … MacLullich, A. M. J. (2014). Validation of the 4AT, a new instrument for rapid delirium screening: a study in 234 hospitalised older people. *Age and Ageing*, *43*(4), 496–502. https://doi.org/10.1093/ageing/afu021

[12] MacLullich A, Ryan T, Cash H. 4AT rapid clinical test for delirium. https://www. the4at. com/. The 4AT. Available online at: https://static1.squarespace.com/static/543cac47e4b0388ca43554df/t/57ebb74ad482e9f4d47b414d/1475065676038/4AT_1.2_English.pdf

[13] Adult Comorbidity Evaluation-27 (ACE-27) Available online at: https://www.rtog.org/LinkClick.aspx?fileticket=oClaTCMufRA%3D&tabid=290

[14] Milne S et al. Adult Comorbidity Evaluation-27 as a predictor of postoperative complications, two-year mortality, duration of hospital stay, and readmission within 30 days in patients with squamous cell carcinoma of the head and neck. British Journal of Oral and Maxillofacial Surgery, Volume 57, Issue 3, 214 – 21

[15] Chaiwat, et al. Postoperative delirium in critically ill surgical patients: incidence, risk factors, and predictive scores. BMC Anesthesiology. 2019;19:39. doi: 10.1186/s12871-019-0694-x

[16] Booka E, Kamijo T, Matsumoto T, et al. Incidence and risk factors for postoperative delirium after major head and neck cancer surgery. J Craniomaxillofac Surg 2016 Jul;44:890–4.

[17] Wang SG, Lee UJ, Goh EK, Chon KM. Factors associated with postoperative delirium after major head and neck surgery. Ann Otol Rhinol Laryngol 2004;113:48–51.

[18] Wood MD, et al Cerebral Oxygenation and Neurological Outcomes Following Critical Illness (CONFOCAL) Research Group, Canadian Critical Care Trials Group,. Low brain tissue oxygenation contributes to the development of delirium in critically ill patients: A prospective observational study. Journal of Critical Care. 2017 Oct;41:289-295. DOI: 10.1016/j.jcrc.2017.06.009.

[19] Mullen JO, Mullen NL. Hip fracture mortality. A prospective, multifactorial study to predict and minimize death risk. Clin Orthop Relat Res 1992;214–22. (280).

[20] Conway, D., Purkayastha, M. & Chestnutt, I. The changing epidemiology of oral cancer: definitions, trends, and risk factors. *Br Dent J* **225,** 867–873 (2018). https://doi.org/10.1038/sj.bdj.2018.922

[21] Shah S, Weed HG, He X, Agrawal A, Ozer E, Schuller DE: Alcohol-related predictors of delirium after major head and neck cancer surgery. Arch Otolaryngol Head Neck Surg 138(3): 266e271, 2012

[22] Yamagata K, Onizawa K, Yusa H, Wakatsuki T, Yanagawa T, Yoshida H: Risk factors for postoperative delirium in patients undergoing head and neck cancer surgery. Int J Oral Maxillofac Surg 34(1): 33e36, 2005

[23] N.A. O'Regan, J. Fitzgerald, S. Timmons, H. O'Connell, D. Meagher, Delirium: A key challenge for perioperative care, International Journal of Surgery, Volume 11, Issue 2, 2013, Pages 136-144, ISSN 1743-9191. https://doi.org/10.1016/j.ijsu.2012.12.015.

[24] Dort JC, Farwell DG, Findlay M, et al. Optimal Perioperative Care in Major Head and Neck Cancer Surgery With Free Flap Reconstruction: A Consensus Review and Recommendations From the Enhanced Recovery After Surgery Society. *JAMA Otolaryngol Head Neck Surg*. 2017;143(3):292-303. doi:10.1001/jamaoto.2016.2981

[25] McMahon J, Handley TPB, Bobinskas A, et al. Postoperative complications after head and neck operations that require free tissue transfer - prevalent, morbid, and costly. *Br J Oral Maxillofac Surg*. 2017;55(8):809-814. doi:10.1016/j.bjoms.2017.07.015

[26] Scottish Delirium Association. Available online at: http://www.scottishdeliriumassociation.com

[27] Alasdair M. J. Maclullich, Atul Anand, Daniel H. J. Davis, Thomas Jackson, Amanda J. Barugh, Roanna J. Hall, Karen J. Ferguson, David J. Meagher, Colm Cunningham, New horizons in the pathogenesis, assessment and management of delirium, *Age and Ageing*, Volume 42, Issue 6, November 2013, Pages 667–674, https://doi.org/10.1093/ageing/aft148

[28] Ishibashi-Kanno N, Takaoka S, Nagai H, et al. Postoperative delirium after reconstructive surgery for oral tumor: a retrospective clinical study [published online ahead of print, 2020 Feb 27]. *Int J Oral Maxillofac Surg*. 2020;S0901-5027(20)30034-5. doi:10.1016/j.ijom.2020.01.018

[29] Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. Lancet 2014; 383: 911–22.

[30] Fong, Tamara G et al. The interface between delirium and dementia in elderly adults The Lancet Neurology, Volume 14, Issue 8, 823 - 832

This is a peer-reviewed, accepted author manuscript of the following research article:
Crawford, J. E., Zubair, F., Baniulyte, G., Wales, C. J., Ansell, M., Thomson, E., Hislop, S., MacIver, C., Devine, J., McCaul, J., Young, D., & McMahon, J. (2020). Postoperative delirium in patients with head and neck oral cancer in the West of Scotland. *British Journal of Oral and Maxillofacial Surgery*. https://doi.org/10.1016/j.bjoms.2020.08.116

Appendix A

DSM V

DSM V Delirium Criteria	
a)	Disturbance in *attention* (i.e., reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced *orientation to the environment*).
b)	The disturbance develops over a short period of time (usually hours to a few days), *represents an acute change from baseline attention and awareness*, and tends to fluctuate in severity during the course of a day.
c)	An additional disturbance in cognition (e.g. memory deficit, disorientation, language, visuospatial ability, or perception).
d)	*The disturbances in Criteria A and C* are not better explained by a pre-existing, established or evolving neurocognitive disorder and *do not occur in the context of a severely reduced level of arousal such as coma.*
e)	There is evidence from the history, physical examination or laboratory findings that the disturbance is *a direct* physiological consequence of another medical condition, *substance intoxication or withdrawal (i.e. due to a drug of abuse or to a medication), or exposure to a toxin, or is due to multiple aetiologies*.

DSM V classification of delirium [3].

ICD 10

ICD 10 Delirium Classification Delirium, not induced by alcohol and other psychoactive substances	
B.	Clouding of consciousness, i.e. reduced clarity of awareness of the environment, with reduced ability to focus, sustain, or shift attention.
C.	Disturbance of cognition, manifest by both:
	1) impairment of immediate recall and recent memory, with relatively intact remote memory;
	2) disorientation in time, place or person.
D.	At least one of the following psychomotor disturbances:
	1) rapid, unpredictable shifts from hypo-activity to hyper-activity;
	2) increased reaction time;
	3) increased or decreased flow of speech;
	4) enhanced startle reaction.
E.	Disturbance of sleep or the sleep-wake cycle, manifest by at least one of the following:
	1) insomnia, which in severe cases may involve total sleep loss, with or drowsiness, or reversal of the sleep-wake cycle;
	2) nocturnal worsening of symptoms;
	3) disturbing dreams and nightmares which may continue as hallucinations illusions after awakening.
F.	Rapid onset and fluctuations of the symptoms over the course of the day.
G.	Objective evidence from history, physical and neurological examination or underlying cerebral or systemic disease (other than psychoactive substance-related) that can be presumed to be responsible for the clinical manifestations in A-D.
Comments: Emotional disturbances such as depression, anxiety or fear, irritability, euphoria, apathy or wondering perplexity, disturbances of perception (illusions or hallucinations, often visual) and transient delusions are typical but are not specific indications for the diagnosis.	

ICD 10 classification of delirium [4].

This is a peer-reviewed, accepted author manuscript of the following research article:
Crawford, J. E., Zubair, F., Baniulyte, G., Wales, C. J., Ansell, M., Thomson, E., Hislop, S., MacIver, C., Devine, J., McCaul, J., Young, D., & McMahon, J. (2020). Postoperative delirium in patients with head and neck oral cancer in the West of Scotland. *British Journal of Oral and Maxillofacial Surgery*. https://doi.org/10.1016/j.bjoms.2020.08.116

Appendix B

4AT

Assessment test for delirium & cognitive impairment

(label)

Patient name:

Date of birth:

Patient number:

Date: **Time:**

Tester:

CIRCLE

[1] ALERTNESS

This includes patients who may be markedly drowsy (eg. difficult to rouse and/or obviously sleepy during assessment) or agitated/hyperactive. Observe the patient. If asleep, attempt to wake with speech or gentle touch on shoulder. Ask the patient to state their name and address to assist rating.

Normal (fully alert, but not agitated, throughout assessment)	0
Mild sleepiness for <10 seconds after waking, then normal	0
Clearly abnormal	4

[2] AMT4

Age, date of birth, place (name of the hospital or building), current year.

No mistakes	0
1 mistake	1
2 or more mistakes/untestable	2

[3] ATTENTION

Ask the patient: "Please tell me the months of the year in backwards order, starting at December." To assist initial understanding one prompt of "what is the month before December?" is permitted.

Months of the year backwards	Achieves 7 months or more correctly	0
	Starts but scores <7 months / refuses to start	1
	Untestable (cannot start because unwell, drowsy, inattentive)	2

[4] ACUTE CHANGE OR FLUCTUATING COURSE

Evidence of significant change or fluctuation in: alertness, cognition, other mental function (eg. paranoia, hallucinations) arising over the last 2 weeks and still evident in last 24hrs

No	0
Yes	4

4 or above: possible delirium +/- cognitive impairment
1-3: possible cognitive impairment
0: delirium or severe cognitive impairment unlikely (but delirium still possible if [4] information incomplete)

4AT SCORE ☐

GUIDANCE NOTES Version 1.2. Information and download: **www.the4AT.com**

The 4AT is a screening instrument designed for rapid initial assessment of delirium and cognitive impairment. A score of 4 or more *suggests* delirium but is not diagnostic: more detailed assessment of mental status may be required to reach a diagnosis. A score of 1-3 suggests cognitive impairment and more detailed cognitive testing and informant history-taking are required. A score of 0 does not definitively exclude delirium or cognitive impairment: more detailed testing may be required depending on the clinical context. Items 1-3 are rated *solely on observation of the patient at the time of assessment*. Item 4 requires information from one or more source(s), eg. your own knowledge of the patient, other staff who know the patient (eg. ward nurses), GP letter, case notes, carers. The tester should take account of communication difficulties (hearing impairment, dysphasia, lack of common language) when carrying out the test and interpreting the score.

Alertness: Altered level of alertness is very likely to be delirium in general hospital settings. If the patient shows significant altered alertness during the bedside assessment, score 4 for this item. **AMT4 (Abbreviated Mental Test - 4):** This score can be extracted from items in the AMT10 if the latter is done immediately before. **Acute Change or Fluctuating Course:** Fluctuation can occur without delirium in some cases of dementia, but marked fluctuation usually indicates delirium. To help elicit any hallucinations and/or paranoid thoughts ask the patient questions such as, "Are you concerned about anything going on here?"; "Do you feel frightened by anything or anyone?"; "Have you been seeing or hearing anything unusual?"

This is a peer-reviewed, accepted author manuscript of the following research article:
Crawford, J. E., Zubair, F., Baniulyte, G., Wales, C. J., Ansell, M., Thomson, E., Hislop, S., MacIver, C., Devine, J., McCaul, J., Young, D., & McMahon, J. (2020). Postoperative delirium in patients with head and neck oral cancer in the West of Scotland. *British Journal of Oral and Maxillofacial Surgery*. https://doi.org/10.1016/j.bjoms.2020.08.116

Appendix C

Adult Comorbidity Evaluation-27

Identify the important medical comorbidities and grade severity using the index.
Overall Comorbidity Score is defined according to the highest ranked single ailment, except in the case where two or more Grade 2 ailments occur in different organ systems. In this situation, the overall comorbidity score should be designated Grade 3.

Cogent comorbid ailment	Grade 3 Severe Decompensation	Grade 2 Moderate Decompensation	Grade 1 Mild Decompensation
Cardiovascular System			
Myocardial Infarct	☐ MI ≤ 6 months	☐ MI > 6 months ago	☐ MI by ECG only, age undetermined
Angina / Coronary Artery Disease	☐ Unstable angina	☐ Chronic exertional angina ☐ Recent (≤ 6 months) Coronary Artery Bypass Graft (CABG) or Percutaneous Transluminal Coronary Angioplasty (PTCA) ☐ Recent (≤ 6 months) coronary stent	☐ ECG or stress test evidence or catheterization evidence of coronary disease without symptoms ☐ Angina pectoris not requiring hospitalization ☐ CABG or PTCA (>6 mos.) ☐ Coronary stent (>6 mos.)
Congestive Heart Failure (CHF)	☐ Hospitalized for CHF within past 6 months ☐ Ejection fraction < 20%	☐ Hospitalized for CHF >6 months prior ☐ CHF with dyspnea which limits activities	☐ CHF with dyspnea which has responded to treatment ☐ Exertional dyspnea ☐ Paroxysmal Nocturnal Dyspnea (PND)
Arrhythmias	☐ Ventricular arrhythmia ≤ 6 months	☐ Ventricular arrhythmia > 6 months ☐ Chronic atrial fibrillation or flutter ☐ Pacemaker	☐ Sick Sinus Syndrome ☐ Supraventricular tachycardia
Hypertension	☐ DBP≥130 mm Hg ☐ Severe malignant papilledema or other eye changes ☐ Encephalopathy	☐ DBP 115-129 mm Hg ☐ DBP 90-114 mm Hg while taking antihypertensive medications ☐ Secondary cardiovascular symptoms: vertigo, epistaxis, headaches	☐ DBP 90-114 mm Hg while not taking antihypertensive medications ☐ DBP <90 mm Hg while taking antihypertensive medications ☐ Hypertension, not otherwise specified
Venous Disease	☐ Recent PE (≤ 6 mos.) ☐ Use of venous filter for PE's	☐ DVT controlled with Coumadin or heparin ☐ Old PE > 6 months	☐ Old DVT no longer treated with Coumadin or Heparin
Peripheral Arterial Disease	☐ Bypass or amputation for gangrene or arterial insufficiency < 6 months ago ☐ Untreated thoracic or abdominal aneurysm (≥6 cm)	☐ Bypass or amputation for gangrene or arterial insufficiency > 6 months ago ☐ Chronic insufficiency	☐ Intermittent claudication ☐ Untreated thoracic or abdominal aneurysm (< 6 cm) ☐ s/p abdominal or thoracic aortic aneurysm repair
Respiratory System			
	☐ Marked pulmonary insufficiency ☐ Restrictive Lung Disease or COPD with dyspnea at rest despite treatment ☐ Chronic supplemental O_2 ☐ CO_2 retention (pCO_2 > 50 torr) ☐ Baseline pO_2 < 50 torr ☐ FEV1 (< 50%)	☐ Restrictive Lung Disease or COPD (chronic bronchitis, emphysema, or asthma) with dyspnea which limits activities ☐ FEV1 (51%-65%)	☐ Restrictive Lung Disease or COPD (chronic bronchitis, emphysema, or asthma) with dyspnea which has responded to treatment ☐ FEV1 (66%-80%)
Gastrointestinal System			
Hepatic	☐ Portal hypertension and/or esophageal bleeding ≤ 6 mos. (Encephalopathy, Ascites, Jaundice with Total Bilirubin > 2)	☐ Chronic hepatitis, cirrhosis, portal hypertension with moderate symptoms "compensated hepatic failure"	☐ Chronic hepatitis or cirrhosis without portal hypertension ☐ Acute hepatitis without cirrhosis ☐ Chronic liver disease manifested on biopsy or persistently elevated bilirubin (>3 mg/dl)
Stomach / Intestine	☐ Recent ulcers(≤ 6 months ago) requiring blood transfusion	☐ Ulcers requiring surgery or transfusion > 6 months ago	☐ Diagnosis of ulcers treated with meds ☐ Chronic malabsorption syndrome ☐ Inflammatory bowel disease (IBD) on meds or h/o with complications and/or surgery
Pancreas	☐ Acute or chronic pancreatitis with major complications (phlegmon, abscess, or pseudocyst)	☐ Uncomplicated acute pancreatitis ☐ Chronic pancreatitis with minor complications (malabsorption, impaired glucose tolerance, or GI bleeding)	☐ Chronic pancreatitis w/o complications

This is a peer-reviewed, accepted author manuscript of the following research article:
Crawford, J. E., Zubair, F., Baniulyte, G., Wales, C. J., Ansell, M., Thomson, E., Hislop, S., MacIver, C., Devine, J., McCaul, J., Young, D., & McMahon, J. (2020). Postoperative delirium in patients with head and neck oral cancer in the West of Scotland. *British Journal of Oral and Maxillofacial Surgery*. https://doi.org/10.1016/j.bjoms.2020.08.116

Cogent comorbid ailment	Grade 3 Severe Decompensation	Grade 2 Moderate Decompensation	Grade 1 Mild Decompensation
Renal System			
End-stage renal disease	☐ Creatinine > 3 mg% with multi-organ failure, shock, or sepsis ☐ Acute dialysis	☐ Chronic Renal Insufficiency with creatinine >3 mg% ☐ Chronic dialysis	☐ Chronic Renal Insufficiency with creatinine 2-3 mg%.
Endocrine System	**(Code the comorbid ailments with the (*) in both the Endocrine system and other organ systems if applicable)**		
Diabetes Mellitus	☐ Hospitalization ≤ 6 months for DKA ☐ Diabetes causing end-organ failure ☐ retinopathy ☐ neuropathy ☐ nephropathy* ☐ coronary disease* ☐ peripheral arterial disease*	☐ IDDM without complications ☐ Poorly controlled AODM with oral agents	☐ AODM controlled by oral agents only
Neurological System			
Stroke	☐ Acute stroke with significant neurologic deficit	☐ Old stroke with neurologic residual	☐ Stroke with no residual ☐ Past or recent TIA
Dementia	☐ Severe dementia requiring full support for activities of daily living	☐ Moderate dementia (not completely self-sufficient, needs supervising)	☐ Mild dementia (can take care of self)
Paralysis	☐ Paraplegia or hemiplegia requiring full support for activities of daily living	☐ Paraplegia or hemiplegia requiring wheelchair, able to do some self care	☐ Paraplegia or hemiplegia, ambulatory and providing most of self care
Neuromuscular	☐ MS, Parkinson's, Myasthenia Gravis, or other chronic neuromuscular disorder and requiring full support for activities of daily living	☐ MS, Parkinson's, Myasthenia Gravis, or other chronic neuromuscular disorder, but able to do some self care	☐ MS, Parkinson's, Myasthenia Gravis, or other chronic neuromuscular disorder, but ambulatory and providing most of self care
Psychiatric			
	☐ Recent suicidal attempt ☐ Active schizophrenia	☐ Depression or bipolar disorder uncontrolled ☐ Schizophrenia controlled w/ meds	☐ Depression or bipolar disorder controlled w/ medication
Rheumatologic	**(Incl. Rheumatoid Arthritis, Systemic Lupus, Mixed Connective Tissue Disorder, Polymyositis, Rheumatic Polymyositis)**		
	☐ Connective Tissue Disorder with secondary end-organ failure (renal, cardiac, CNS)	☐ Connective Tissue Disorder on steroids or immunosuppressant medications	☐ Connective Tissue Disorder on NSAIDS or no treatment
Immunological System	**(AIDS should not be considered a comorbidity for Kaposi's Sarcoma or Non-Hodgkin's Lymphoma)**		
AIDS	☐ Fulminant AIDS w/KS, MAI, PCP (AIDS defining illness)	☐ HIV+ with h/o defining illness. $CD4^+ < 200/\mu L$	☐ Asymptomatic HIV+ patient. ☐ HIV^+ w/o h/o AIDS defining illness. $CD4^+ > 200/\mu L$
Malignancy	**(Excluding Cutaneous Basal Cell Ca., Cutaneous SCCA, Carcinoma in-situ, and Intraepithelial Neoplasm)**		
Solid Tumor including melanoma	☐ Uncontrolled cancer ☐ Newly diagnosed but not yet treated ☐ Metastatic solid tumor	☐ Any controlled solid tumor without documented metastases, but initially diagnosed and treated within the last 5 years	☐ Any controlled solid tumor without documented metastases, but initially diagnosed and treated > 5 years ago
Leukemia and Myeloma	☐ Relapse ☐ Disease out of control	☐ 1st remission or new dx <1yr ☐ Chronic suppressive therapy	☐ H/o leukemia or myeloma with last Rx > 1 yr prior
Lymphoma	☐ Relapse	☐ 1st remission or new dx <1yr ☐ Chronic suppressive therapy	☐ H/o lymphoma w/ last Rx >1 yr prior
Substance Abuse	**(Must be accompanied by social, behavioral, or medical complications)**		
Alcohol	☐ Delirium tremens	☐ Active alcohol abuse with social, behavioral, or medical complications	☐ H/o alcohol abuse but not presently drinking
Illicit Drugs	☐ Acute Withdrawal Syndrome	☐ Active substance abuse with social, behavioral, or medical complications	☐ H/o substance abuse but not presently using
Body Weight			
Obesity		☐ Morbid (i.e., BMI ≥ 38)	

OVERALL COMORBIDITY SCORE (Circle one.)	**0** **None**	**1** **Mild**	**2** **Moderate**	**3** **Severe**	**9** **Unknown**