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Non-smoking, non-drinking, oral squamous cell carcinoma patients are a distinct and clinically significant group

Abstract

Carcinogenesis of oral squamous cell carcinoma (OSCC) has long been associated with exposure to tobacco smoke and alcohol consumption. Some centres have reported that non-smoking non-drinking (NSND) patients represent a significant and increasing proportion of OSCC cases with reports of poorer outcomes. Demographic characteristics are variably reported for this group and carcinogenesis is not fully understood. We present the largest cohort study to date in this subject area. We interrogated 541 OSCC patients by retrospective analysis to assess risk factor status, disease characteristics and survival. Patients were categorised according to smoking and alcohol exposure with non-smoker (NS) status defined as less than five cigarettes per week with no history of use greater than this. Non-drinker (ND) status was defined as less than three standard drinks per week with no history of alcohol consumption greater than this. Those both NS and ND were categorised as NSND. Subsite, tumour stage and treatment were recorded along with evidence of cervical nodal and distant metastasis. NSNDs comprise a significant proportion our OSCC population. These patients were more likely to be female, older and present with early-stage disease. Tumour site was tongue, maxillary alveolus and buccal mucosa, at variance with the smoker drinker groups. Thus, NSNDs are a clinically distinct and significant group in oral cavity cancer management.

Keywords: Oral cancer; squamous cell carcinoma; non-smoking; non-drinking; survival; epidemiology.

Introduction

Head and neck cancers are the sixth commonest cancer world-wide with oral subtypes accounting for almost half (48%) of case and most oral tumours (90%) being oral squamous cell carcinomas (OSCC).[1] Treatment normally includes surgery, resulting in significant morbidity, with 5-year overall survival reported as low as 41%.[2] Tobacco and alcohol consumption are independent risk factors, however when taken together they synergistically increase risk 8 to 15-fold .[3] OSCC is most likely to affect males in their fifth and sixth decades with a history of tobacco and alcohol consumption.[4] , There is a developing body of evidence of increasing cases of oral cavity cancer occurring in non-smokers and nondrinkers (NSND). This group is known to comprise 15-35% of the OSCC population and has a different aetiology and appears to have differing clinical presentation. NSNDs are more likely to be female and some reports have reflected worse overall survival. Tongue and gingival tumours are reported to be more common in NSNDs whereas the floor of the mouth and retromolar trigone are more common in smokers and drinkers (SD). [5-9]

Many studies in the literature do not consider OSCC in isolation, instead focusing on head and neck cancers as a whole or grouping both oral and oropharyngeal cancers together. Within the NSND cohort several subgroups have been identified such as elderly females (>70 years, NSNDEF) who are reported to have significantly decreased disease-specific survival and a higher rate of recurrence.[5, 6] Additionally, an increase in young NSNDs (<40 years, YNSND) has been reported along with a *young tongue cancer syndrome* and evidence that these patients have underwent more aggressive treatment despite not having worse prognoses.[10, 11]

Differing clinicopathological characteristics observed in NSNDs suggests a unique aetiology separate from traditional risk factors. There has been intense focus surrounding the role of Human Papillomavirus (HPV) infection however it is now understood that whilst this may account for a small proportion of cases it cannot explain the rapid increase in incidence. Other sexually transmitted pathogens such as HSV-2 may still be implicated in the rising incidence, particularly the oral tongue, in younger patients.[12-14] This may represent changes in societal sexual behaviour as has been implicated in oropharyngeal cancer.[15] However, this is unlikely to explain the emergence of the elderly NSND cohort, suggesting a distinct aetiology. Recent evidence links a dysbiotic oral microbiome with increased OSCC risk with periodontal pathogens known to be associated with carcinogenesis in NSNDs.[16] *Fusobacterium nucleatum and Porphyromonas gingivalis* are among those currently being investigated.[17] Other factors such as an enhanced tumour microenvironment may be suggestive of an immunological aetiology and a potential role for immunotherapy in these individuals.[12] Additionally, it may be that a proportion of cases occur as a result of an as yet undefined genetic predisposition. This is considered to be insufficient to explain data reflecting rapidly increasing incidence. We have to date failed to identify a single causative agent, therefore multiple factors may be involved in a complex aetiopathogenesis.

Reports of emerging NSND cohorts with poorer survival give further impetus to the need to both understand aetiology and enable preventive strategies and also to identify such patients early and facilitate timely intervention for cure. Accurately defining the clinicopathological features of NSND disease is central to identifying both aetiological processes and any potential for altered treatment regimes.

This study was to interrogate by retrospective analysis a cohort of OSCC patients presenting within the Queen Elizabeth University Hospital between 2015 and 2018 for demographic factors, risk factor status and clinical disease history. We also compare overall survival of NSND patients with the cohort carrying traditional risk factors.

Materials and Methods

Data collection and classification

A retrospective analysis of 541 patients with OSCC treated within the Department of Maxillofacial Surgery between January 2015 to December 2018 was carried out with patients identified by assessing records of weekly MDT meetings. Clinical notes were accessed with selection criteria limited to diagnosis of OSCC and an identifiable risk factor status available. Demographic and disease related data were gathered with patients categorised according to smoking and alcohol exposure. NS status defined as less than five cigarettes per week with no history of use greater than this and ND status as less than three standard drinks per week with no history of alcohol consumption greater than this. Combined risk factor status was then assigned with those both NS and ND recorded as NSND. Those with a history of smoking or alcohol consumption were recorded as smoker and / or drinker (SD).[5, 6] American Joint Committee on Cancer 8th edition, tumour staging data was recorded along with an International Classification of Disease (ICD-10) subsite. Carcinomas of the lip, soft palate, uvula, palatine and lingual tonsils, base of tongue and oropharyngeal sub-sites were excluded. Evidence of cervical nodal spread or distant metastasis was recorded. Survival time was assessed with respect to the census date of the 20th of February 2021. Patients were followed-up for a minimum of 26 months. Where patients were still alive or lost to follow-up they were

recorded as censored. All-cause mortality was assessed as disease-specific survival data were unavailable.

Statistical analysis

Statistical analysis was performed using the statistical package SPSS (Version 27.0).

Categorical disease characteristic data were analysed by Pearson's chi-square test (χ^2) with Student's *t*-test utilised for age distribution analyses. Univariate survival analyses were performed using Kaplan-Meier survival curves and Log-Rank tests for significance with Cox proportional hazards survival regression utilised for multivariate survival analysis. Only those factors found to be univariately significant were entered into the multivariate model. Statistical significance was set at $p<0.05$.

Results

Patient demographics

From the 541 patients identified, 113 (20.9%) were NSNDs. Males were 321 (59.3%) and females were 220 (40.7%). The overall mean age at diagnosis was 66.5 years (median 67.0 years) with NSNDs more likely to be older than SDs (mean 70.0 vs 65.6 years, p=0.004, *t*test,). Females were more likely to be NSND than males with 77 (35.0%) females identified as NSND compared to 36 (11.2%) males (χ^2=44.69, p<0.001) (Table 1). NSNDEF were 50 (9.2%) and YNSND were 5 (0.9%) .

Individually, NS were 139 (25.7%) and ND were 207 (38.3%). Most females (60.9%) were NDs and a majority of males (77.3%) were drinkers (χ^2=80.50, p<0.001). Whilst the majority of both males and females were smokers, females were less likely to be smokers than males (61.8% vs 82.9%, χ^2=30.29, p<0.001).

Subsite and stage

NSNDs were more likely to have tumours of the tongue (χ^2=5.36, p=0.021), maxillary alveolus (χ^2=8.63, p=0.003) and buccal mucosa (χ^2=12.21, p<0.001). SDs were more likely to have floor of mouth (χ^2=31.14, p<0.001) and retromolar trigone tumours (χ^2=6.97, p=0.008). The tongue was the commonest subsite in the YNSND group (*n*=4, 80%), however the small sample size (*n*=5) precluded significance testing (Table 2).

Tumour stage was generally evenly distributed despite less patients presenting with stage III (*n*=68, 12.6%). NSNDs were more likely to have stage I disease, (χ^2=11.25, p<0.001) whereas SDs were more likely to present with stage IV (χ^2=4.05, p=0.044) (Table2). Positive cervical nodes were present in 213 patients however no significant links to NSND status were noted despite an increased risk observed for drinkers compared to NDs (χ^2=6.89, p=0.009). Distant metastasis was observed in 8 patients, all of whom were SDs with stage IV disease.

Treatment

NSNDs were more likely to undergo primary surgery than SDs (χ^2=4.36, p=0.037) with no other significant differences observed (Table 2).

Univariate survival analysis

The mean survival time for all patients was 29.4 months with a median of 30.0 months ranging from 0.0–73.0 months. Half of our patients had died by the census date (*n*=271, 50.1%). Two patients (0.4%) were lost to follow up.

Smokers had significantly decreased overall survival compared to NSs (p=0.017, Log-Rank (Fig. 3). Both local cervical node and distant metastasis, along with elderly status were significant for decreased survival (p<0.001, Log-Rank). Increasing tumour stage was significant for decreased survival when considered both individually (I vs II etc.) as well early vs late-stage disease (I/II vs III/IV) (p<0.001, Log-Rank). Treatment modality was also significant (p<0.001. Log-Rank)

A trend towards reduced survival was noted in SDs compared to NSNDs however this did not achieve statistical significance (p=0.059, Log-Rank)(Fig. 1). NSNDEF status was not significant for decreased survival (p=0.718) (Fig. 2). There was no difference in survival between males and females. Alcohol status was also not significant, as well as there being no evidence for a difference in survival between subsites (all p>0.05, Log-Rank)(Fig. 4).

Multivariate survival analysis

Tumour stage (expressed as stage I/II vs III/IV), cervical nodal spread, elderly status and smoking status were univariately significant and therefore entered into the multivariate model. Distant metastasis was not included due to small sample size; inclusion however had little effect. Treatment was omitted due to there being confounding variables and small numbers of patients receiving certain treatments. All factors remained significant for decreased survival with multivariate analysis (p<0.05).

Discussion

These data support the hypothesis that NSNDs are a significant group with clinically distinct characteristics. We did not find evidence of reduced overall survival for NSND patients, with an insignificant trend being observed in the opposite direction. Cases of OSCC in YNSND did not comprise a significant proportion of our patients, despite growing reports in the literature.[8, 10]

In our series NSNDs were more likely to have tongue, maxillary alveolus and buccal mucosa tumours and this concurred with previous literature. Oral tongue as by far the most common subsite aligns with the growing focus on oral tongue cancer in NSNDs as a distinct disease.[5, 6, 10, 11] A direct carcinogenic effect on the mucosa of the retromolar trigone from inhaled cigarette smoke could explain the high proportion of tumours that we identified in this subsite in smokers. Additionally, dissolved carcinogens pooling on the floor of the mouth has been described to produce a direct carcinogenic effect, with ethanol providing solvent to facilitate access of carcinogens to mucosal cells. It has also been reported that cigarette smoke and saliva have a synergistic effect upon oral cancer risk.[18, 19] These factors could perhaps explain why we found these subsites to be more common in smokers.

We found NSNDs to be older where others have reported a younger mean age.[20] Koo et al. described a bimodal age distribution with peaks in the fifth and seventh decades.[5] Our cohort is significantly larger (*n*=541 vs *n*=169) but did not replicate this finding. Nevertheless, we present strong evidence that NSNDEF are clinically significant.

That NSND status was not significant for reduced overall survival has been reported previously, with some reporting that NSNDs have better overall survival. Further, it is

intuitive that these patients are likely to have better overall health than SDs.[21-23] Treatment is often aggressive and multi-morbid - SDs tend to have worse outcomes.[24] However, our finding is in contrast to others reporting worse survival for this group.[5, 6] Despite reporting worse overall survival for NSNDs in 2013, a 2021 follow up study consisting of the same patient cohort, Koo et al. failed to replicate this finding on multivariate analysis.[5, 25] This highlights that even within a single centre NSND status is not a steadfast predictor for survival.

To date there has not been universal criteria for a NS or a ND. Alcohol consumption is often underappreciated. Gormley et al. suggest the carcinogenic burden may be highly dependent upon the individual. Mutations in aldehyde dehydrogenase result in certain individuals being unable to adequately breakdown the carcinogenic ethanol metabolite acetaldehyde. The frequency of this mutation is low in most populations however many other genes are involved in ethanol metabolism. Polymorphisms here may explain why some experience a significantly higher 'burden' from lower levels of ethanol, including mouthwashes.[26] A significant proportion of our patients (38.3%), including most females (60.9%) were NDs. Further research into ethanol metabolism may redefine our understanding of safe quantities for different individuals.

In Scotland, successful national campaigns have seen smoking and drinking rates fall, and the suggestion has been made that the increase in NSND OSCC cases is a reflection of this.[27] Against this argument is the ongoing rise of cases of head and neck cancer, despite reducing risk factor behaviour in our population and increased over the population rate in the rest if the United Kingdom. Certainly, the proportion of NSND oral cavity cancers is expected to rise in the future as the longer-term effects of decreased consumption manifest.

Quantifying changes in societal risk factor prevalence may prove essential to understanding the NSND epidemic. Smokeless tobacco and vapour devices including electronic cigarettes have been recommended as smoking cessation adjuncts and are also commonly used by younger individuals who have never smoked.[28] The nicotine delivery vapour in such devices does not contain the flat chain hydrocarbon carcinogens found in tobacco smoke and hence some authorities recommend these as part of a harm reduction programme. The longer-term effects of exposure to such devices remains to be evaluated over time. This is not sufficient to explain the current rise in NSND patients however it may, in time, result in more cases of risk factor negative OSCC.

We worked to maximise accuracy of data analysed in this study. To that end, multiple sources were consulted to ensure accurate risk factors status was achieved. We acknowledge that it was not possible to quantify secondary risk factors which may represent significant confounding variables, e.g., living with a smoker and some occupations. Secondhand smoke exposure is also inherently difficult to quantify, particularly with older cohorts. The majority of our patients were white-British individuals with a minority of other ethnic groups. The role of ethnicity was therefore not assessable.

Conclusion

NSNDs comprise a significant proportion our OSCC population. These patients were more likely to be female, older and present with early-stage disease. Tumour site was tongue, maxillary alveolus and buccal mucosa, at variance with the smoker drinker groups. Thus, NSNDs are a clinically distinct and significant group in oral cavity cancer management.

Conflict of Interest

We have no conflicts of interest.

Ethics statement/confirmation of patient permission

Our retrospective study did not require ethics committee approval. No such consent was required as no patient identifying data were included

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Table 1

Combined risk factor status by gender.

	NSND (*n*=113) *n* (% of total gender)	SD (*n*=428) *n* (% of total gender)
Male** (*n*=321)	36 (11.2)	285 (88.8)
Female**(*n*=220)	77 (35.0)	143 (65.0)

*p < 0.05, ** p < 0.001 (Pearson's χ^2 test).

Table 2

Summary of patient characteristics, subsite, T stage, treatment.

	NSND *n* (% of total NSND)	SD *n* (% of total SD)
Site:		
Floor of mouth**	3 (2.7)	116 (27.1)
Mandibular alveolus	15 (13.3)	41 (9.6)
Maxillary alveolus*	12 (10.6)	16 (3.7)
Tongue*	58 (51.3)	168 (39.3)
Hard palate	3 (2.7)	7 (1.6)
Retromolar trigone*	5 (4.4)	57 (13.3)
Buccal mucosa**	17 (15.0)	23 (5.4)
T-stage:		
T1**	46 (40.7)	106 (24.8)
T2	26 (23.0)	103 (24.1)
T3	10 (8.8)	58 (13.6)
T4*	31 (27.4)	161 (37.6)
Treatment: Palliative		
care	24 (21.2)	125 (29.2)
Surgery*	61 (54.0)	184 (43)
Adjuvant radiotherapy	24 (21.2)	90 (21.0)
Adjuvant chemoradiotherapy	3 (2.7)	20 (4.7)
Primary radiotherapy	1 (0.9)	6 (1.4)
Primary chemoradiotherapy	0 (0.0)	3 (0.7)

*p < 0.05, ** p < 0.001 (Pearson's χ^2 test).

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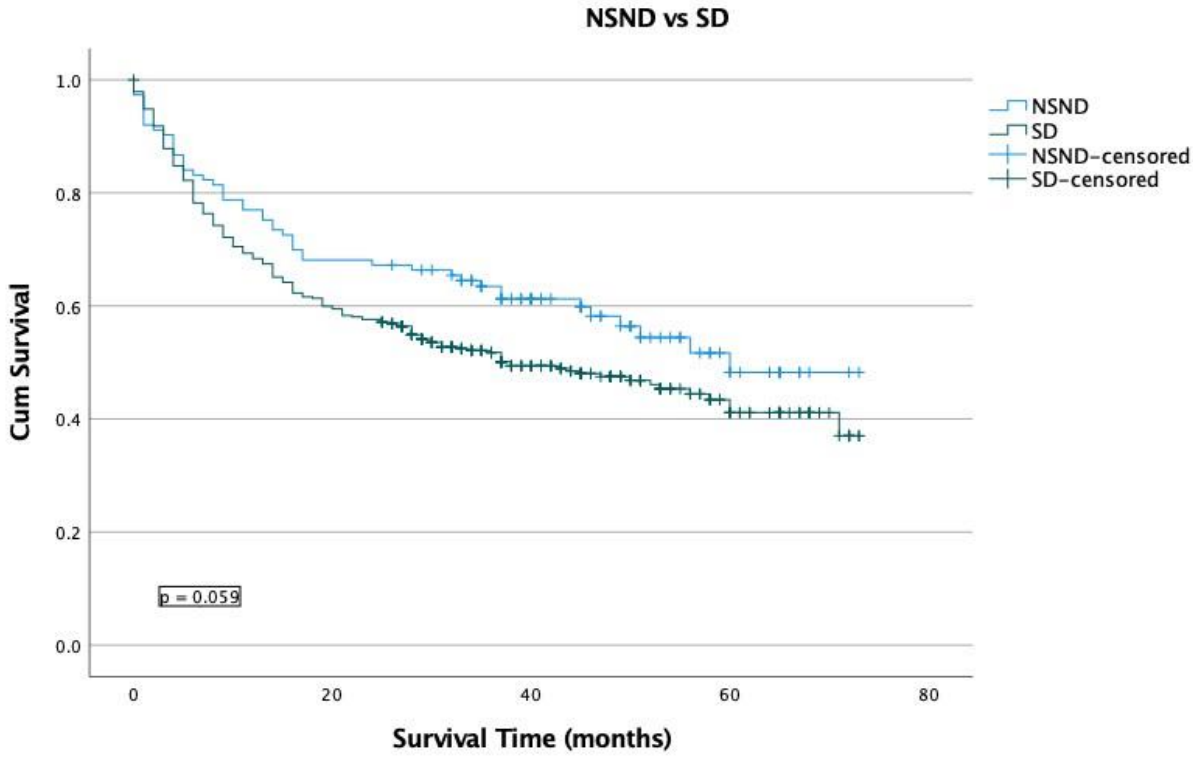

Fig.1 Survival by NSND status.

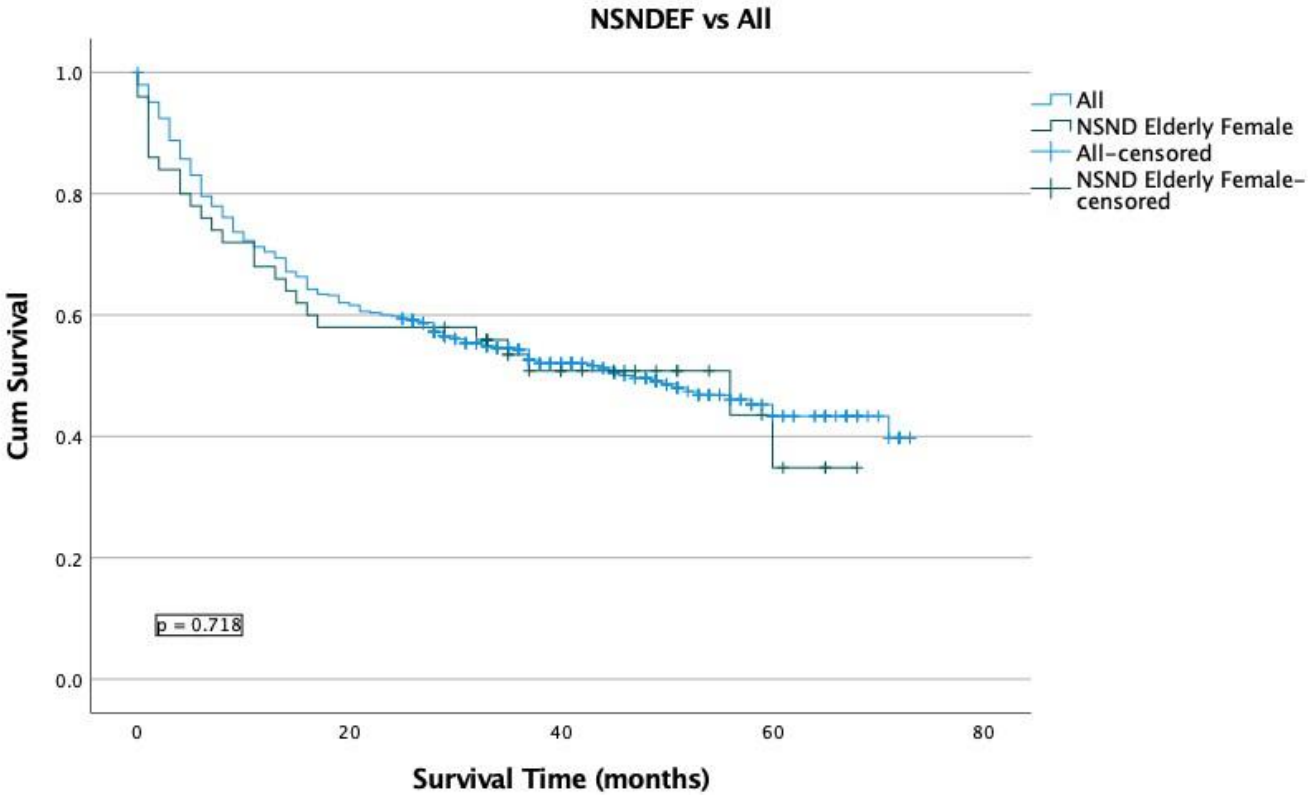

Fig 2. Survival of NSNDEFs.

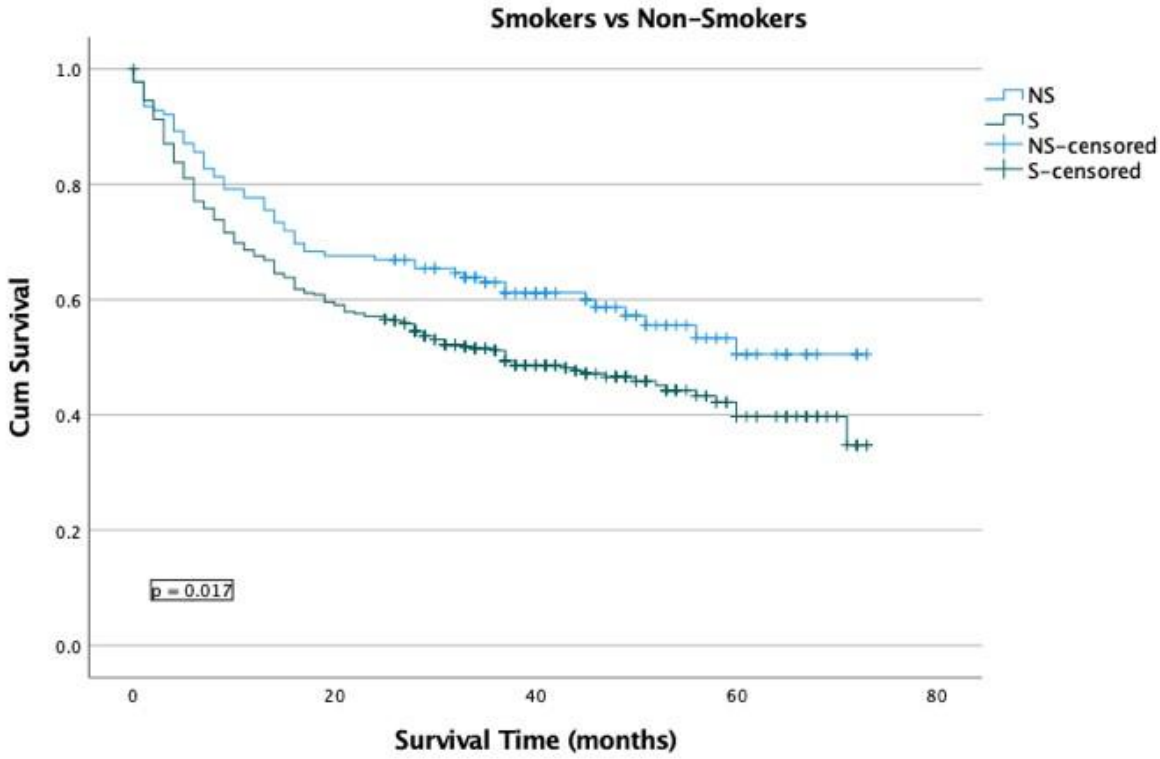

Fig3. Survival by smoker status.

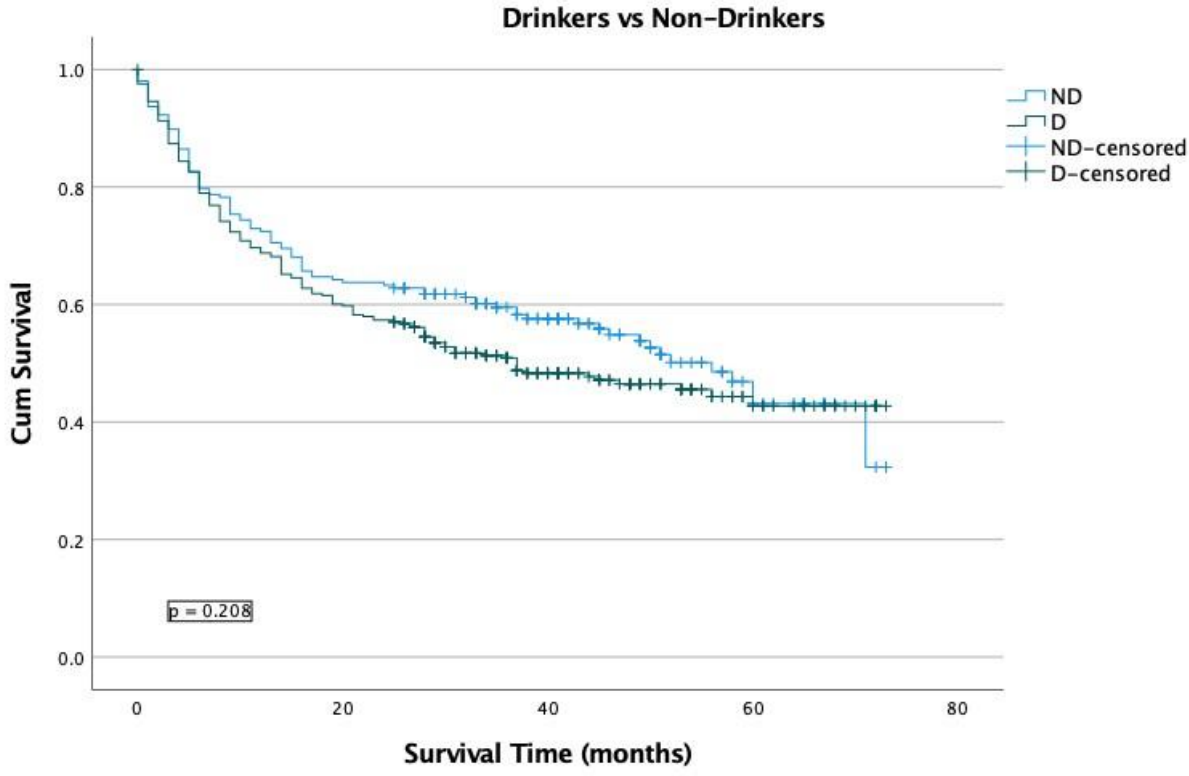

Fig.4 Survival by alcohol status