Impact of Tobacco, Marijuana, and Alcohol use on Overall Survival in Recurrent Metastatic head and neck Cancer Patients Treated with Immune Checkpoint Inhibitors

Mohammad Bilal Alsavaf
The Ohio State University Wexner Medical Center
Majd Issa
The Ohio State University Wexner Medical Center
Brett G Klamer
The Ohio State University
Marium Husain
The Ohio State University Wexner Medical Center
Khaled Dibs
The Ohio State University Wexner Medical Center
Xueliang Pan
The Ohio State University
John C Grecula
The Ohio State University Wexner Medical Center
Matthew O Old
The Ohio State University Wexner Medical Center
David Konieczkowski
The Ohio State University Wexner Medical Center
Darrion L Mitchell
The Ohio State University Wexner Medical Center
Sujith Baliga
The Ohio State University Wexner Medical Center
Ricardo L Carrau
The Ohio State University Wexner Medical Center
James W Rocco
The Ohio State University Wexner Medical Center
Marcelo Bonomi
The Ohio State University Wexner Medical Center
Dukagjin M. Blakaj
The Ohio State University Wexner Medical Center

Priyanka Bhateja (Priyanka.Bhateja@osumc.edu)
The Ohio State University Wexner Medical Center

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Abstract

Background:

The response rates to immune checkpoint inhibitors (ICI) remain low (13-20%) in metastatic head and neck cancer patients and better understanding of factors predictive of response to these agents is urgently needed. Here we explore the impact of smoking status, marijuana use and alcohol on treatment outcomes in recurrent-metastatic (R/M) head and neck squamous cell carcinoma (HNSCC) treated with ICI.

Methods:

We performed a retrospective analysis of 201 R/M HNSCC patients treated with ICI between January 15th 2016 and April 9th 2020 at a single institution.

Results:

Gender: 154 male (77%), 47 female (23%). Median age 61 (IQR: 55-68). ICI drug: pembrolizumab 100 (50%), nivolumab 91 (45%), nivolumab+ipilimumab 10 (5%). Line of therapy: first: 98 (49%), second and beyond: 103 (51%). Tumor site: oropharynx 84 (42%), oral cavity 45 (22%), larynx 26 (13%), other sites 46 (23%). p16 tumor status: negative 132 (66%), positive 69 (34%). Smoking status: former 111 (55%), never 54 (27%), current 36 (18%), median pack-year 18 (IQR: 0-37). Alcohol use: yes 110 (55%), no 91 (54%). Marijuana use: yes 47 (23%), no 154 (77%). Overall response rate: 36 (18%). Median OS: 12 months (95% CI: 9.4-14.8). Tobacco: former (HR: 0.75, 95% CI: 0.50, 1.11), current (HR: 0.58, 95% CI: 0.33, 1.02). Marijuana: yes (HR: 0.93, 95% CI: 0.58, 1.49). Alcohol: yes (HR: 1.04, 95% CI: 0.72, 1.49).

Conclusion:

In our cohort, smoking status, marijuana use and alcohol consumption did not have a statistically significant impact on OS in patients with R/M HNSCC treated with ICI.

Trial registration: retrospectively registered.

Background:

Head and neck cancer is the sixth most prevalent cancer worldwide, with squamous cell carcinoma being the dominant histology. It has a 50–60% fatality rate and carries a significant economic burden to health systems around the globe (1). Annually, the incidence of new cases diagnosed is increasing worldwide (1–4). Typically, these tumors arise from the mucosal epithelium of pharynx, oral cavity and larynx (5). Human papillomavirus (HPV) infection has been established as an important risk factor for tumors originating from the oropharynx, while tobacco use, alcohol consumption and other environmental

factors are strongly linked to the formation of HPV-negative cancers (6, 7, 16, 8–15). There is still some controversy regarding whether or not marijuana usage is a risk factor, and a portion of this debate can be attributed to confounding risk factors (17–19).

Given their survival benefit, the US Food and Drug Administration (FDA) has approved ICI in the form of anti-programmed cell death protein 1 (a-PD 1) for treatment of R/M HNSCC (20–23). Currently, Pembrolizumab is approved in the first line setting, while both Pembrolizumab and Nivolumab are approved as second-line therapies following progression on platinum-based treatment. Approximately 13 to 20 percent of patients will experience clinical benefit, while the majority will progress within the first two years of commencing ICI (22–24). Hence, numerous studies were conducted in order to better identify candidates who are more likely to benefit from treatment with ICI, and researchers have explored clinical characteristics, inflammatory markers and prognostic survival models (25, 26). Besides, identifying the effect of modifiable lifestyle habits and metabolic disorders on ICI results is crucial to maximizing the outcomes (27).

Among the modifiable factors, there is limited data addressing smoking, alcohol consumption, and diet, but to the best of our knowledge, no data has been published regarding the relationship between marijuana use and the outcome of ICI treatment for R/M HNSCC. In the scientific literature, there is conflicting data between modifiable risk factors and survival rate in patients treated with ICI, which raises the likelihood of missing confounding variables. There have been both significant and non-significant reports about the link between alcohol consumption and OS (28, 29). Intriguingly, smoking demonstrated improved survival in lung squamous cell carcinoma but worse survival in HNSCC (30). In melanoma patients, obesity was also associated with contradictory outcomes (31–34). The focus of this retrospective analysis is to assess the impact of smoking, alcohol, and marijuana use on OS in this patient population.

Materials And Methods:

This is an Institutional Review Board-approved retrospective analysis of a single institutional cohort of R/M HNSCC patients treated with at least one dose of a-PD1 antibody in the first, second-line (or beyond), between January 15th, 2016, and April 9th, 2020. Inclusion criteria were age over 18 and pathologically diagnosed HNSCC in the oropharynx, oral cavity, larynx, hypopharynx, nasopharynx, and paranasal sinuses, or a HNSCC p-16 positive tumor of unknown origin. Patients with incomplete treatment records, uncertain tumor histology, those who received concurrent ICI with chemotherapy, and those treated with ICI in the context of a clinical trial were excluded from the final analysis. We collected data regarding smoking status, marijuana usage, and alcohol consumption while on ICI. Smoking status was identified as one of the following: active, former or never. Active smoker was defined as a person who currently smoked at least one cigarette a day, former smoker was defined as a person who quit smoking at the time of starting ICI. Marijuana use was defined as the consumption of cannabis, either by smoking, vaping or ingestion at least once a week while on ICI. Alcohol use was defined as one or more drinks per week while on ICI. OS was defined from the start of ICI to death.

Statistical analysis:

Patient characteristics were summarized using descriptive statistics. The Kaplan-Meier estimate was used for visualization of overall survival and unadjusted differences in overall survival by tobacco, marijuana, and alcohol usage. The log-rank test was used for unadjusted comparison of overall survival between groups. Separate Cox proportional hazard regression models were fit for each of the tobacco, marijuana, and alcohol exposure variables. Each model adjusted for age, sex, albumin, hgb, lymphocytes, ldh, neutrophils, and P-16 status. Statistical significance was defined at an alpha level of 0.05. All statistical analyses were performed using R version 4.2.2 with the survival (version 3.5-0) package.

Results:

We Analyzed data for a total of 223 pts, that initiated treatment with ICI between January 15th 2016 and April 9th 2020, as first, second or further line of therapy. 201 pts met our inclusion criteria. There were 154 males (77%) and 47 females (23%), with a median age of 61 (IQR: 55–68). One hundred eleven pts (55%) were former smokers, 54 had never smoked (27%), and 36 were current smokers (18%), with a median pack-year of 18 (IQR: 0–37). One hundred and ten pts used alcohol (55%), while 47 used marijuana (23%) during the course of treatment with ICI. Sixty-nine pts (34%) had a P-16 positive tumor. A total of 84 (42%) tumors originated in the oropharynx, followed by 45 (22%) oral cavity, 26 (13%) larynx and 46 (23%) malignancies originated from other sites. One hundred (50%) pts received pembrolizumab, 91 (45%) nivolumab, and 10 (5%) received a combination of nivolumab with ipilimumab. Ninety-eight (49%) pts received ICI as their first line of therapy, while 102 (51%) as a second line and beyond (Table 1). Tables stratified by substance use are provided in the supplement. One hundred and twenty-four (62%) pts had progressed while treated with ICI, with 64 (32%) of them received subsequent chemotherapy. The most common type of recurrence on ICI was observed in distant sites in 83 (53%) pts. At the time of this analysis, 135 (67%) pts had expired. Overall response rate was 36 (18%). The median follow-up time was 10 months (IQR: 3, 19) and the median OS for the entire cohort was 12 months (95% CI: 9.4, 14.9) (Fig. 1). Compared to pts who had never smoked tobacco, former smokers (HR: 0.75, 95% CI: 0.50, 1.11) and current smokers (HR: 0.58, 95% CI: 0.33, 1.02) each had reduced hazard of death on the adjusted model (global p = 0.14). Marijuana users had reduced hazard (HR: 0.93, 95% CI: 0.58, 1.49) compared to pts who did not use marijuana. Alcohol consumption resulted in increased hazard (HR: 1.04, 95% CI: 0.72, 1.49) compared to those who did not consume. (Fig. 2). Though smoking status, marijuana use, and alcohol consumption did not have a statistically significant impact on OS in this patient population, we found the direction of effect to be favorable of survival for both tobacco users and marijuana use.

Table 1
Patient characteristics

Characteristic	N = 201[1]
Sex	
Male	154 (77%)
Female	47 (23%)
Age (Years)	61 (55, 68)
Tumor Site	
Oropharynx	84 (42%)
Oral Cavity	45 (22%)
Larynx	26 (13%)
Other	46 (23%)
ICI Line of Therapy	
First Line	98 (49%)
Second Line and Beyond	103 (51%)
ICI Drug	
Pembrolizumab	100 (50%)
Nivolumab	91 (45%)
Nivolumab + Ipilimumab	10 (5.0%)
ECOG	
0	36 (18%)
1	96 (48%)
2	53 (26%)
3	16 (8.0%)
Tobacco use	
Never	54 (27%)
Former	111 (55%)
Current	36 (18%)
Marijuana use	

Characteristic	N = 201[1]
Sex	
No	154 (77%)
Yes	47 (23%)
Alcohol use	
No	91 (45%)
Yes	110 (55%)
P-16 Status	
Negative	132 (66%)
Positive	69 (34%)
Albumin	
Normal	156 (78%)
Low	45 (22%)
HGB	
Normal	101 (50%)
Low	100 (50%)
Lymphocytes	0.69 (0.47, 1.08)
LDH	
Normal	124 (62%)
High	77 (38%)
Neutrophils	4.58 (3.43, 6.47)
P-16 Status	
Negative	132 (66%)
Positive	69 (34%)
Response	
CR	32 (16%)
PR	4 (2.0%)
SD	41 (20%)

Characteristic	N = 201[1]
Sex	
PD	124 (62%)
[1]n (%); Median (IQR)	

Discussion:

Cigarette smoking and excessive alcohol consumption have been found to be major risk factors for HPV-negative HNSCC, and their combination has synergistic carcinogenic effects (35). The decrease in smoking rates and the rise of HPV-associated HNSCC in western countries, contribute to the improved outcomes in this patient population (5, 36, 37). However, in certain tumor types such as NSCLC, smokers appear to have better response to ICI compared to never smokers (38–40). One possible explanation for this is that TTF-1 (thyroid transcription factor-1) expression is lower among non-smokers, who are more prone to acquire poorly differentiated lung cancers (41, 42). Despite some discrepancy, there is mounting evidence that links TTF-1 expression to improved ICI efficacy and programmed death-ligand 1 (PD-L1) expression (43–46). Never smokers also have a high incidence of EGFR mutations or anaplastic lymphoma kinase (ALK) rearrangements (47–50), where ICIs are known to be less effective. A further explanation for the superior response to ICI in lung cancer smokers than in HNSCC smokers is that smoking's proinflammatory effect is more pronounced in lung cancer, but its immunosuppressive effect is more prominent in HNSCC (30). In accordance with previous findings, we observed no significant impact of smoking on the survival rate of HNSCC patients treated with ICI.

Overexpression of PD-L1 has been discovered to contribute to T cell exhaustion in persistent infections (51). In similar manner, the expression of PD-L1 by cancers allows them to evade the immune system by downregulating T cells (52). Although PD-1/PD-L1 blockade ICI improved overall survival in a variety of PD-L1-expressing tumors, efficacy remains limited for the vast majority of patients (53). Several studies have demonstrated that nicotine use increases PD-L1 expression (54, 55). Zeleskis et al. showed that smokers had improved immunotherapy efficacy, unless they quit smoking, in which case a rapid rebound effect resulting in decreased PD-L1 expression. Moreover, authors demonstrated that early chemotherapy induces a more consistent high level of PD-L1 expression after cascading chemotherapy (56). However, studies suggest that only increasing the expression of PD-L1 in well-responding tumors would maximize the effectiveness of ICI treatment (57–59). Yang et al. indicated that smoking signature was a better predictor of pathological response in patients with non-small cell lung cancer (NSCLC) than expression of (PD-L1) (60). Preliminary analysis of earlier studies revealed that PD-L1 is expressed in 50–66% of HNSCC and that tumor infiltration by PD-1-positive CD8 lymphocytes, PD-1-positive CD4 lymphocytes, and PD-1-positive Tregs was more prevalent in HPV-positive HNSCCs than in HPV-negative HNSCCs (61–63). In one recent trial, pembrolizumab alone or with chemotherapy significantly increased OS in R/M HNSCC patients with PD-L1 combined positive score (CPS) ≥ 1 (64).

Alcohol consumption appears counterproductive for the ICI since it suppresses the innate immune response by diminishing cell recruitment and disrupting macrophage phagocytosis activity (65–67). It also interferes with T cell stimulation by suppressing the expression of CD80 and CD86 on dendritic cells and reducing their quantity (68, 69). A greater expression of PD-1 on T cells has been reported in individuals with acute alcoholic hepatitis, although we doubt this has a positive effect on ICI due to the aforementioned effects (70). A prior study revealed that the immunological milieu of oral squamous cell carcinoma (OSCC) patients who never smoked or consumed alcohol ,was enhanced with PD-L1 and CD8 T cell infiltration and had a better response to ICI (28). In contrast, another study showed the opposite results for the same type of cancer, with no significant correlation between alcohol consumption and response to ICI (29). In our cohort, we observed no significant impact of alcohol consumption on the OS rate of R/M HNSCC patients treated with ICI. Acute alcohol exposure in mice was reported to stimulate anti-inflammatory cytokine production, but the opposite effect was reported in alcoholic hepatitis patients secondary to a short term of heavy consumption (71, 72). Alcohol consumption also causes gut microbiota shifts and bacterial changes (73–76). There is growing understanding on the impact of gut microbiota as a modulator of efficacy and tolerability of ICI (77). Researchers have found evidence of microbial alteration of anticancer immune responses after transplanting fecal microbiota in vivo (78, 79).

In the past decade, medicinal marijuana has become increasingly prescribed due to its potential benefits as a relaxant, anxiolytic, anti-inflammatory antidepressant, antiemetic, and pain reliever, but it also has several potential side effects (80–86). Some studies have indicated a correlation between cannabinoid and an increase in tumor growth (87, 88). Synthetic agonists of cannabinoids increase the activity of PI3K/AKT and MAP signaling pathway (89). The association between marijuana use and development of head and neck cancer remains controversial. Gillison et al. reported evidence of an association between marijuana use and HPV + HNSCC, while Liang et al. demonstrated that moderate marijuana use significantly reduced the risk of HNSCC in those who began using it later in life (90, 91). Cannabinoid receptors represent a complex pathway and interact with immune system at various levels. Given marijuana use in transplant recipients and auto-immune disorders like ulcerative colitis and rheumatoid arthritis there is concern about potential interaction with ICIs. Hence, with the growing use of marijuana, studies that aim to evaluate the potential association of marijuana use with outcomes in cancer patients improve shared decision making. A survey based study found that about one fourth of cancer patients had high active cannabis use but did not receive information about cannabis use from their oncology providers(92). The growing use of cannabis in palliative oncology and a lack of comfort from oncology providers about discussing cannabis use, highlights the importance of studies like ours that explore potential effect or interaction of cannabis with commonly used oncology treatments.

Active ingredients of cannabis can affect several biological processes and human body also produces endogenous analogs of these ingredients. The complex signaling system composed of these ligands and multiple receptors regulates several physiological processes, including the innate and adaptive immune functions. By influencing immune functions cannabinoids can regulate auto-immunity, inflammation, and antitumor immune response. The endocannabinoid system prevents pathological immune responses and is regarded as the gate keeper. On the level of the bone marrow, cannabis causes the retention of

immature B cells, a considerable reduction in CXCR4, and suppression of lymphocyte recovery (93–95). Cannabinoids affect various cellular and cytokine processes leading to immune suppression. There is a four-prong mechanism that leads to these effects: induction of apoptosis (of T cells, macrophages, splenocytes, and thymocytes) (88), inhibition of cell proliferation, inhibition of production of chemokines and cytokines, and induction of T-regs (96, 97). CBD induced CD4 + and CD8 + cell apoptosis is proposed to occur through increased reactive oxygen species generation and increased caspase activity (98). In invitro experiments, human eosinophils T, B, CD-8, and NK cells decrease cytokine production after activation in response to CBD exposure (99). Other proposed mechanisms of reduction of T-cell immunity against cancer by cannabis involve blocking downstream JAK1-STAT signaling (100).

Studies evaluating the interaction of marijuana use on ICI treatment have shown varied results. Biedney et al. and Bar-Sela et al. revealed a substantial connection between cannabis usage during ICI treatment and poorer OS, which they attributed to the anti-inflammatory effects of cannabinoids (101, 102). Bar-Sela et al. also showed a substantial reduction in the time to tumor advancement and a decrease in immune-related side effects (102). Contrarily, Taha et al. found no difference in progression-free survival or OS despite a lower response rate (103). The lack of statistically significant interaction between marijuana and outcomes in patients getting ICI in our study could potentially be due to sample size, under reporting of marijuana use by patients or dose dependent relationship with marijuana use due to the complex ligand and receptor pathway. It is also possible that providers pay less attention to a detailed marijuana history. Within the limitations of a single center retrospective study, we hypothesize that marijuana use in head and neck cancer patients does not modulate the immune system enough to impact outcomes with ICI treatment. Future independent studies should aim to evaluate the interactions between marijuana use, dose intensity and outcomes with various cancer treatments, especially ICI.

Limitation:

This study provides valuable data regarding the effects of cigarette smoking, alcohol drinking, and marijuana use on OS in a large cohort of R/M HNSCC patients treated with ICI. This sort of publication is essential for developing treatment strategies and correlating clinical findings with molecular-level research. Since our study is a single-institution retrospective investigation, the results may not generalize to the overall population of patients. There are evident conflicting findings among the prior studies, calling for a large-scale pooling of data or metanalysis of the existing data to give a more definitive conclusion. Our cohort did not include genetic or IHC studies, such as PD-L1 expression or tumor mutational load, which we will add to future research.

Conclusion:

Our single institution cohort provides useful information regarding smoking status, marijuana usage, and alcohol consumption in relation to OS in patients with R/M HNSCC treated with ICI. According to our knowledge, this is the first study to investigate the impact of marijuana use on ICI therapy in HNSCC patients. Further comprehensive and multicentric studies are warranted to validate these results.

Abbreviations:

(ICI) checkpoint inhibitors; (R/M) recurrent-metastatic; (HNSCC) head and neck squamous cell carcinoma; (OS) overall survival; (HPV) Human papillomavirus; (FDA) Food and Drug Administration; (a-PD 1) death protein 1; (ALK) anaplastic lymphoma kinase; (PD-L1) death-ligand 1; (NSCLC) non-small cell lung cancer; (CPS) combined positive score; (OSCC) oral squamous cell carcinoma.

Declarations:

Institutional Review Board Statemen:

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board of The Ohio State University and Wexner medical center (No. 2013H0197). Informed consent requirement was waived by the Institutional Review Board of the Ohio State University and Wexner medical center due to the study's observational retrospective design.

Consent for publication

Not applicable.

Data availability:

All raw data are available in case of a reasonable request from the corresponding author.

Competing interests:

The authors declare that they have no competing interests.

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Author Contributions:

Mohammad Bilal Alsavaf, Majd Issa and Priyanka Bhateja interpreted the results and contributed to manuscript writing. Brett Klamer and Xueliang Pan analyzed the data and prepared the figures. Marcelo Bonomi, Marium Husain, James W Rocco, Ricardo L Carrau, Matthew O Old, David Konieczkowski, John C Grecula, Khaled Dibs, Sujith Baliga and Darrion L Mitchellcared for the patients and revised the Manuscript. Marcelo Bonomi, Majd Issa, Priyanka Bhateja, and Dukagjin M. Blakaj designed the study, read and revised the manuscript.

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Figures

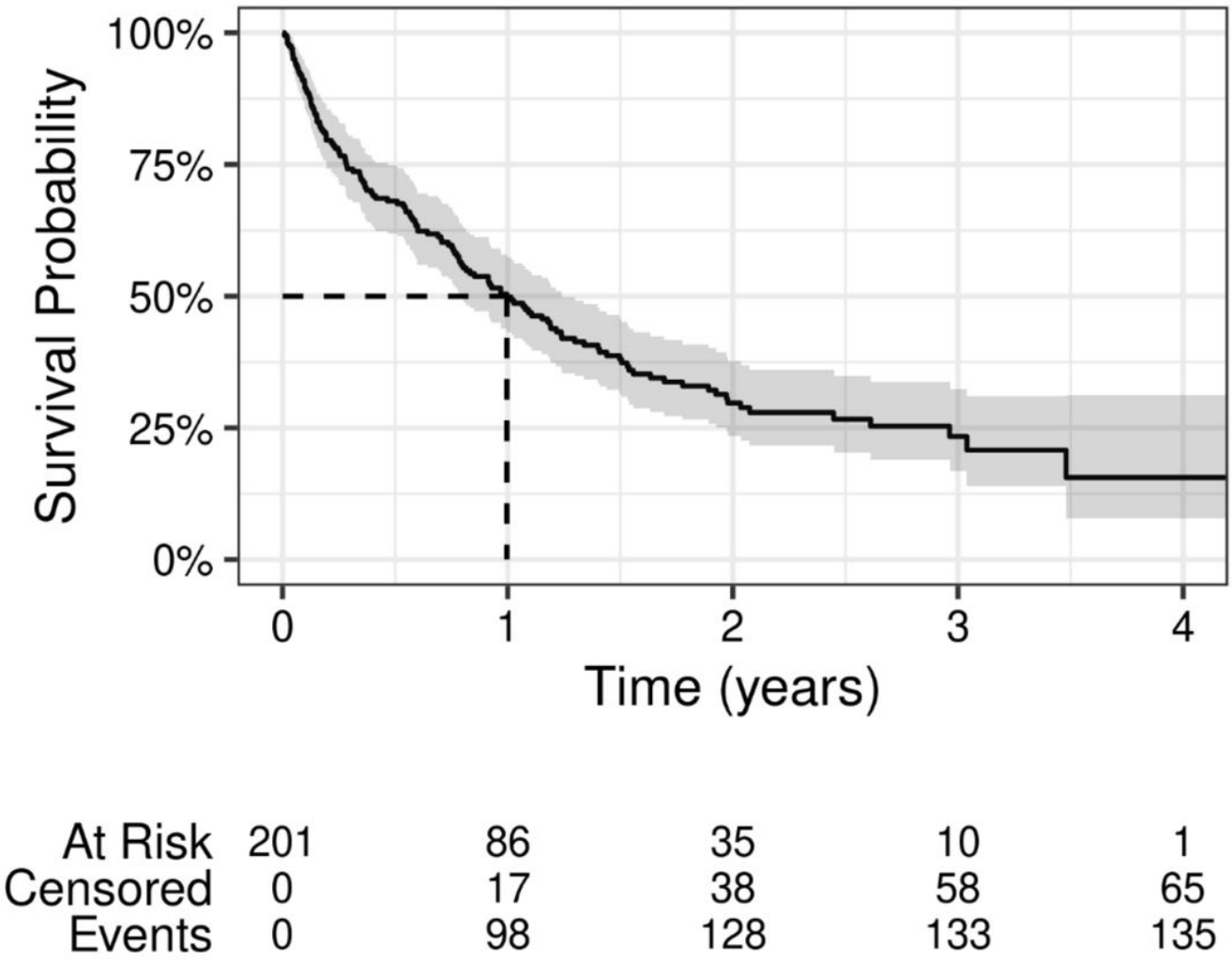

Figure 1

Kaplan-Meier estimate of overall survival for the entire cohort.

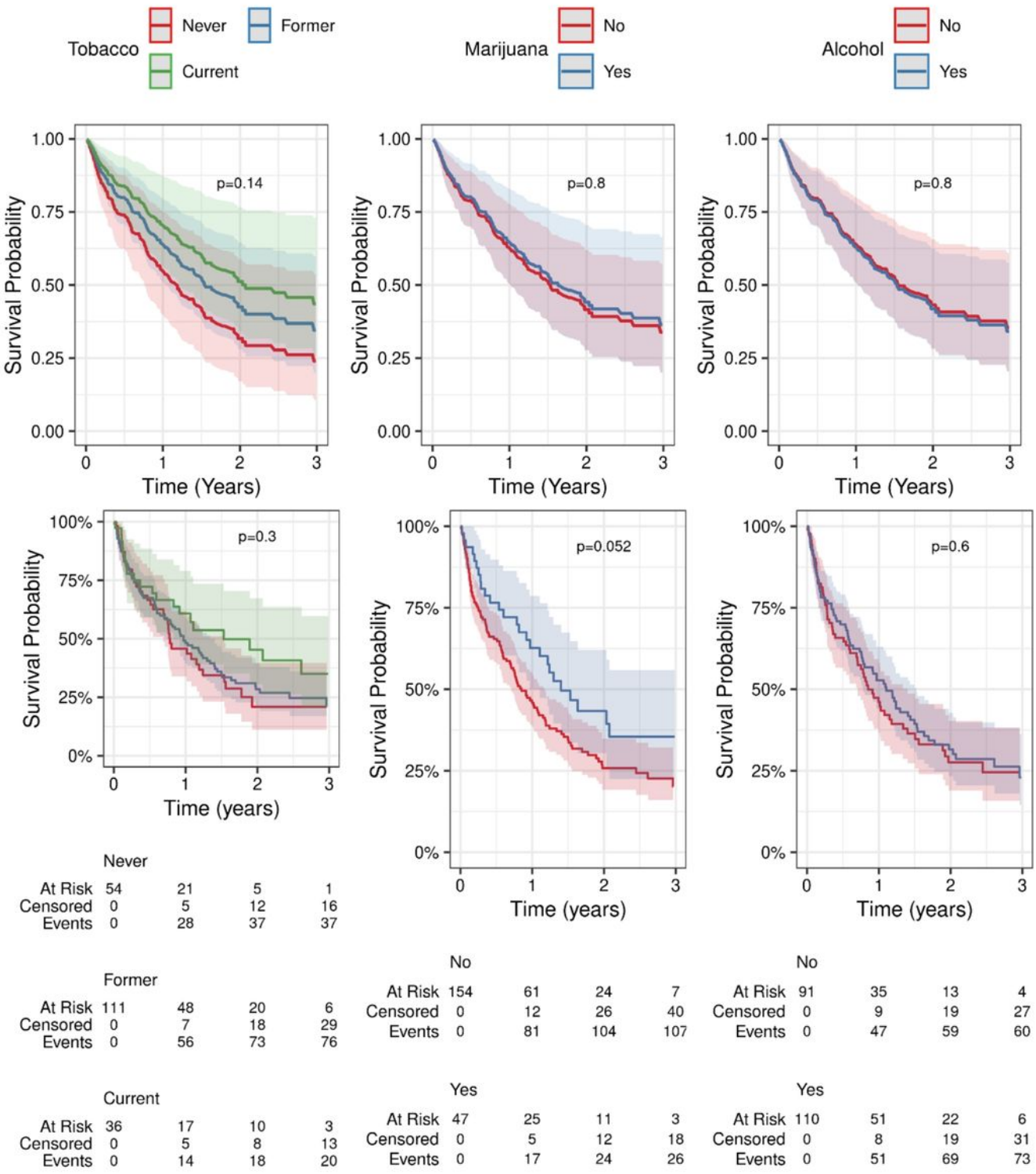

Figure 2

Overall survival estimates stratified by substance use. Each column shows survival outcomes by tobacco, marijuana, and alcohol use, respectively. The first row of figures provide the conditional, Cox proportional hazards estimates. These survival outcomes are conditioned on age=61, sex=Male, neutrophils=5.6 K/uL, lymphocytes=0.87 K/uL, albumin=Normal, hgb=Normal, LDH=Normal, and P-16 status=Negative. The second row of figures provides the observed Kaplan-Meier estimated survival outcomes.

Supplementary Files

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- TableS1.docx
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