Biomedicines

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Universities and research institutions in Switzerland

Media Ranking in Switzerland

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- Biochemistry, Genetics and Molecular Biology (miscellaneous)

Medicine
- Medicine (miscellaneous)

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INFORMATION

Homepage

How to publish in this journal

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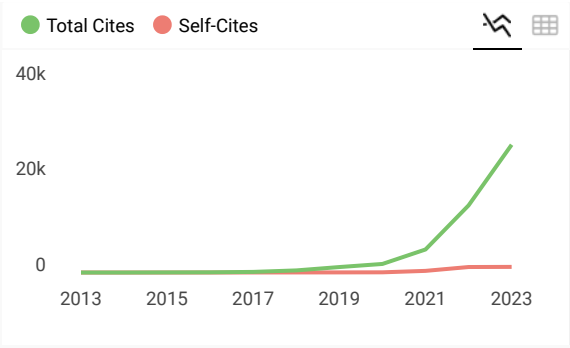
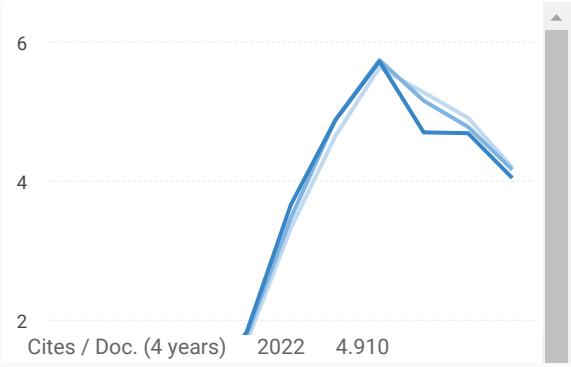
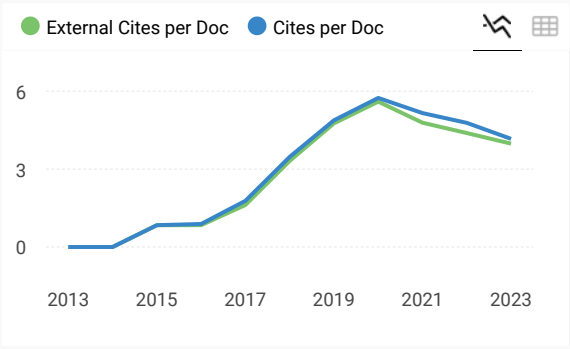
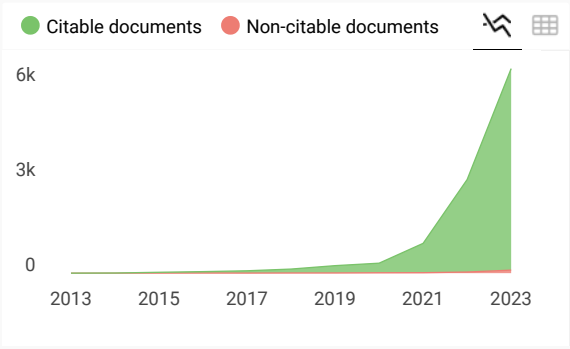
SCOPE

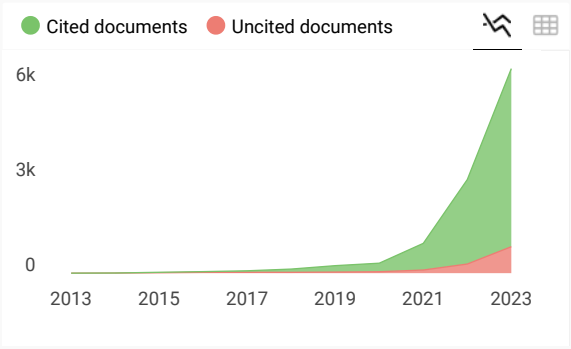
Biomedicines (ISSN 2227-9059) is an open access journal devoted to research of naturally driven biomedicines, pharmaceuticals, and biopharmaceutical products. The topics include natural bioactive molecules, biologics, biosimilar, vaccines, gene therapies, cell-based therapies, targeted specific antibodies, recombinant therapeutic proteins, nanobiotechnology driven products, targeted therapy, bioimaging, biosensors, biomarkers, nano-similars, and nano-biosimilars. The journal is open for publication of studies conducted at the basic science, clinical development and clinical trial stages. Also, publications that address safety, pharmacovigilance regulatory, and ethical issues are welcome. We invite you to consider submitting your work to Biomedicines, be it original research, review articles, or developing special issues of current key topics. The aim of Biomedicines is publishing high quality papers that address the challenges in bringing biological agents or novel targeted strategies through identification, developmentand ultimately to clinical use. Therefore,

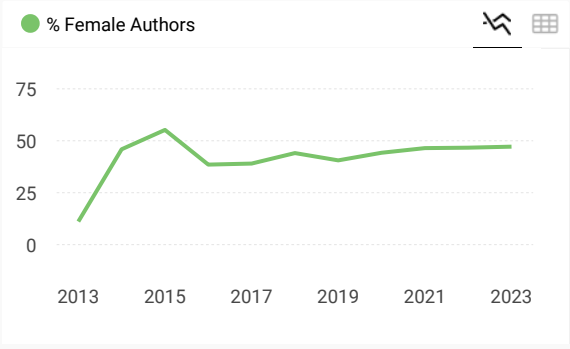


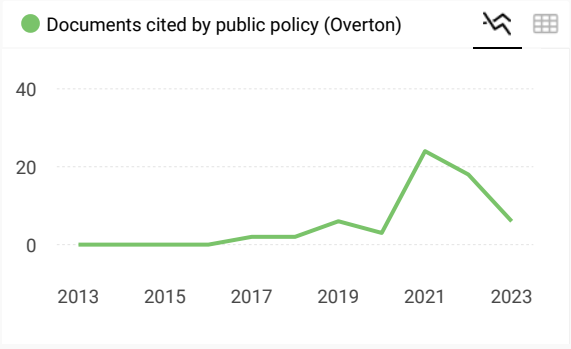


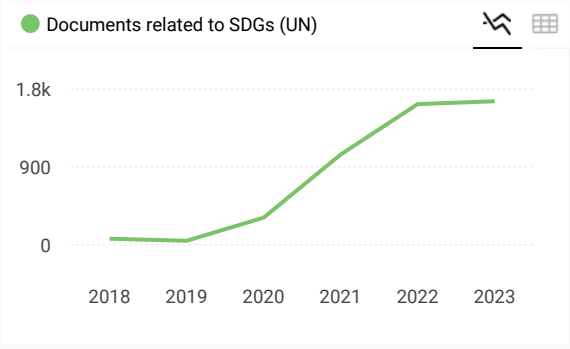


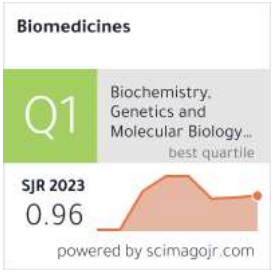












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Members

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Prof. Dr. Ricardo E. Pérez-Tomás
Website (http://www.ub.edu/cellbiology/lab-members-member/ricardo-enrique-perez-tomas/)
Section Board Member
Department of Pathology and Experimental Therapy, Faculty of Medicine, University of Barcelona, Campus de Bellvitge., Lab.5101 C./ Feixa Llarga s/n E- 08907, Hospitalet de Llobregat, Barcelona, Spain
Interests: new molecules for cancer chemotherapy; apoptosis; signal transduction for cancer chemotherapy

Dr. Sara M. Piccirillo

Website (https://hsc.unm.edu/directory/piccirillo-sara.html)

Section Board Member

Department of Cell Biology and Physiology, University of New Mexico Health Sciences Center, Albuquerque, NM 87131, USA

Interests: glioblastoma; cancer stem-like cells; stem cell & tumor cell biology; cancer genomics

Dr. Matthew Pincus

Website (https://doctor.webmd.com/doctor/matthew-pincus-28cd78c2-dec5-11e7-9f4c-005056a225bf-overview)

Section Board Member

Department of Pathology, SUNY Downstate Medical Center, 450 Clarkson Avenue, Brooklyn, NY 11203, USA

Interests: anti-cancer peptides; molecular modeling of oncogenic and anti-oncogenic proteins; ras-p21 protein; p53 protein; PNC-27 anti-cancer peptide; membrane-bound HDM-2 protein; trans-membrane pore formation in cancer cells; ras-p21 peptides; selective blockade of oncogenic ras-p21 protein

Special Issues, Collections and Topics in MDPI journals

Prof. Dr. Francesco Piva

Website (https://www.researchgate.net/profile/Francesco-Piva)

Section Board Member

International Head and Neck Scientific Group, 35030 Padua, Italy

Interests: pancreatic ductal adenocarcinoma; exosomes; tumor microenvironment; targeted therapy; RNA-seq data analysis; artificial neural networks

Dr. Rong-Jiang Qin

Website (https://orcid.org/0000-0002-8559-616X)

Section Board Member

Institute of Basic Medicine and Cancer, Chinese Academy of Sciences (CAS), Hangzhou, China

Interests: gastric cancer; UPS; small molecule inhibitors; targeted protein degradation; traditional Chinese medicine

Special Issues, Collections and Topics in MDPI journals

Dr. Claudio Remondelli

Website (https://docenti.unisa.it/005665/curriculum)

Section Board Member

Department of Medicine, Surgery and Dentistry “Scuola Medica Salernitana”, University of Salerno, Via Salvador Allende, 84081 Baronissi, Italy

Interests: vesicular trafficking; unfolded protein response; endoplasmic reticulum stress; ER mitochondria interplay; neurodegenerative disorders; cancer

Special Issues, Collections and Topics in MDPI journals

Dr. Giulia Ricci

Website (http://www.medicinasperimentale.unicampania.it/dipartimento/docenti/pagina-personale-dei-docenti/item/51-ricci-giulia)

Section Board Member

Department of Experimental Medicine, Second University of Naples, Naples, Italy

Interests: reproduction; embryonic development; cancer; biomaterials; space biology

Special Issues, Collections and Topics in MDPI journals

Dr. Elisa Rumi

Website (https://www.researchgate.net/profile/Elisa_Rumi)

Section Board Member

1. Department of Molecular Medicine, University of Pavia, 27100 Pavia, Italy
2. Hematology, Fondazione IRCCS Policlinico San Matteo, 27100 Pavia, Italy

Interests: myeloproliferative neoplasms; polycythemia vera; thrombocythemia; myelofibrosis

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Dr. Jason K. Sa

Website (https://koreauniv.pure.elsevier.com/en/persons/kyungha-sa)

Section Board Member

Department of Biomedical Sciences, Korea University College of Medicine, Seoul 02841, Republic of Korea

Interests: cancer biology and therapeutic section; molecular genetics and genetic disease section; pharmacogenomic and personalized medicine section potential topics: cancer genomics; tumor evolution; glioblastoma

Special Issues, Collections and Topics in MDPI journals

Prof. Dr. Daniele Santini

Website (https://phd.uniroma1.it/web/DANIELE-SANTINI_nC3371_IT.aspx)

Section Board Member

Department of Radiological Sciences, Oncology and Pathology, Sapienza University of Rome, 00161 Rome, Italy

Interests: GU cancers; immunotherapy in cancer; supportive therapy in cancer; bone health and bone metastases

Special Issues, Collections and Topics in MDPI journals

Dr. Akinori Sato

Website1 (https://www.researchgate.net/profile/Akinori-Sato-4) Website2 (https://publons.com/researcher/1372214/akinori-sato/)

Section Board Member

Department of Urology, National Defense Medical College, Tokorozawa, Japan

Interests: endoplasmic reticulum stress; histone acetylation; protein ubiquitination; autophagy; drug repositioning; tumor metabolism; molecular biology

Dr. Fuyuki Sato

Website (https://www.researchgate.net/profile/Fuyuki-Sato)

Section Board Member

Department of Diagnostic Pathology, Shizuoka Cancer Center, 1007 Shimonagakubo, Nagaizumi-cho, Sunto-gun, Shizuoka Prefecture 411-8777, Japan

Interests: crosstalk between circadian rhythm and tumor progression; pathological analysis in human and mouse tissues; functional analysis of DEC1 and DEC2 in tumor progression; molecular pathways of DEC1 and DEC2; crosstalk between basic and clinical research, involving clock genes

Special Issues, Collections and Topics in MDPI journals

Dr. Nicola Silvestris

Website (https://www.researchgate.net/profile/Nicola_Silvestris)

Section Board Member

1. Medical Oncology Unit, IRCCS Istituto Tumori “Giovanni Paolo II”, 70124 Bari, Italy
2. Department of Human Pathology in Adulthood and Childhood Gaetano Barresi, University of Messina, 98125 Messina, Italy

Interests: translational research (predictive and prognostic markers in gastrointestinal malignancies); treatment of gastrointestinal malignancies; conduction of clinical trials

Dr. Ferenc Sipos

Website (https://doktori.hu/index.php?menuid=192&lang=EN&sz_ID=9965)

Section Board Member

Department of Internal Medicine and Hematology, Semmelweis University, Budapest, Hungary

Interests: innate immunity; TLR9-signaling; autophagy; inflammation and cancer; inflammatory bowel disease; colorectal cancer; mucosal regeneration; immunology; gastroenterology; internal medicine

Special Issues, Collections and Topics in MDPI journals

Dr. Ryszard Smolarczyk

Website (https://cdnio.io.gliwice.pl/en/experimental-therapy-group/)

Section Board Member

Center for Translational Research and Molecular Biology of Cancer, Maria Skłodowska-Curie National Research Institute of Oncology, Gliwice Branch, Wybrzeże Armii Krajowej Street 15, 44-102 Gliwice, Poland

Interests: anti-cancer therapy; tumor blood vessels; vascular disrupting agents (VDAs); tumor microenvironment; combined therapy; radiotherapy; tumor targeting drugs; polymer drug nanocarriers; hypoxia; cell therapy

Special Issues, Collections and Topics in MDPI journals

Dr. Chunhua Song

Website (https://sites.psu.edu/stemcellhershey/chunchua-song-phd/)

Section Board Member

1. Hershey Medical Center, Pennsylvania State University Medical College, Hershey, PA 17033, USA
2. Division of Hematology, The Ohio State University Wexner Medical Center, The James Cancer Hospital, Columbus, OH 43210, USA

Interests: leukemia; pediatric ALL; Ikaros, stem cell; epigenetics; cell signaling

Special Issues, Collections and Topics in MDPI journals

Dr. Khalid Sossey-Alaoui

Website (https://case.edu/cancer/members/member-directory/khalid-sossey-alaoui)

Section Board Member

1. Department of Medicine, Rammelkamp Center for Research, Cleveland, OH 44109, USA
2. Case Western Reserve University School of Medicine, Cleveland, OH 44106, USA

Interests: breast cancer; TNBC; cancer stem cells; tumor immune evasion; invasion-metastasis cascade; EMT; immunotherapy; tumor microenvironment

Dr. Kenichi Suda

Website (https://www.kindai.ac.jp/english/research/researchers/introduce/suda-kenichi-d18.html)

Section Board Member

Division of Thoracic Surgery, Department of Surgery, Kindai University Faculty of Medicine, Osaka-Sayama 589-8511, Japan

Interests: lung cancer; circulating tumor DNA; liquid biopsy; acquired resistance mechanism

Special Issues, Collections and Topics in MDPI journals

Prof. Dr. Antoni M. Szczepanik

Website (https://sportmedicum.pl/en/doctors/chirurg-chirurg-onkologiczny-prof-uj-dr-hab-antoni-szczepanik-2/)

Section Board Member

1st Department of Surgery, Medical College, Jagiellonian University, Krakow, Poland

Interests: surgical oncology; immunology; nutrition; colorectal cancer; gastric cancer

Special Issues, Collections and Topics in MDPI journals

Prof. Dr. Catherine Thieblemont

Website (https://www.metacan.eu/teachers/catherine-thieblemont/)

Section Board Member

1. Haematology, University of Paris, Paris, France
2. Department of Hemato-Oncology, Hospital Saint-Louis, 75010 Paris, France

Interests: the biological and clinical features of lymphomas; targeted therapies; immunotherapies and CAR T cells; genomic and metabolomic studies on low and high grade lymphomas

Dr. Mangesh Thorat

Website (https://www.kcl.ac.uk/people/mangesh-thorat)

Section Board Member

Queen Mary, University of London, London, UK
Interests: cancer; breast cancer; translational research; biomarkers

Dr. Riccardo Vago
Website (https://research.hsr.it/en/institutes/urological-research-institute/extracellular-vescicles-and-toxins/riccardo-vago.html)
Section Board Member
1. School of Medicine, Università Vita-Salute San Raffaele, Milano, Italy
2. IRCCS San Raffaele Scientific Institute, Milano, Italy
Interests: extracellular vesicles; exosomes; therapeutic toxins; targeted cancer therapy; cancer-associated long non-coding RNA

Prof. Dr. Jan B. Vermorken
Website (https://www.oncology-central.com/expert-panel/jan-b-vermorken/)
Section Board Member
1. Department of Medical Oncology, Antwerp University Hospital, 2650 Edegem, Belgium
2. Faculty of Medicine and Health Sciences, University of Antwerp, 2610 Antwerp, Belgium
Interests: head and neck oncology; gynecologic oncology; clinical pharmacology; clinical trials; HPV
Special Issues, Collections and Topics in MDPI journals

Dr. Michele I. Vitolo
Website (https://www.medschool.umaryland.edu/profiles/Vitolo-Michele/)
Section Board Member
Department of Pharmacology, Greenebaum National Cancer Institute Comprehensive Cancer Center, University of Maryland School of Medicine, 655 West Baltimore St., Bressler Research Bldg., Rm. 10-039, Baltimore, MD 21201, USA
Interests: breast cancer; metastasis; cytoskeletal; PTEN; PI3K; circulating tumor cells (CTCs)
Special Issues, Collections and Topics in MDPI journals

Prof. Dr. Satoshi Wada
Website (https://nrid.nii.ac.jp/nrid/1000030420102/)
Section Board Member
Department of Clinical Diagnostic Oncology, Showa University Clinical Research Institute for Clinical Pharmacology and Therapeutics, 6-11-11 kita-karasuyama, setagaya-ku, Tokyo 157-8577, Japan
Interests: cancer immunotherapy; biomarker; CAR-T; Immune checkpoint inhibitor; pancreatic cancer
Special Issues, Collections and Topics in MDPI journals

Dr. Hiroshi Wakao
Website (https://loop.frontiersin.org/people/254816/network)
Section Board Member
Division of Host Defense, Center for Frontier Medicine, Dokkyo Medical University, Mibu 321-0293, Japan
Interests: MAIT cells; iPS cells; regenerative medicine; innate immunity; bacterial/viral infection;

asthma; DM; obesity; cancer; immunotherapy; adoptive transfer

Special Issues, Collections and Topics in MDPI journals

Dr. Ori Wald

Website (https://www.researchgate.net/scientific-contributions/Ori-Wald-39241717)

Section Board Member

Hebrew University Faculty of Medicine and Department of Cardiothoracic Surgery, Hadassah Hebrew University Hospital, Ein-Kerem, Jerusalem, Israel

Interests: thoracic malignancies; thoracic surgery

Dr. Gabriela Wilhelm

Website (http://www.brc.hu/en//research/institute-of-biophysics/molecular-neurobiology-research-unit/neurovascular-unit-research-group)

Section Board Member

Institute of Biophysics, Biological Research Centre, Eötvös Loránd Research Network (ELKH), 6726 Szeged, Hungary

Interests: blood-brain barrier; neurovascular unit; cerebral endothelium; pericytes; tight junctions; signaling; brain metastases; melanoma, breast cancer, metastatic niche, proteases, exosomes, miRNAs, neuroinflammation

Dr. Alberto Zambelli

Website (https://www.hunimed.eu/it/member/alberto-zambelli/)

Section Board Member

Medical Oncology Unit, Azienda Ospedaliera Papa Giovanni XXIII, 24127 Bergamo, Italy

Interests: breast cancer; breast cancer translational research; prognostic and predictive breast cancer biomarkers; breast cancer new drug development

Special Issues, Collections and Topics in MDPI journals

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Website (https://old.ug.edu.pl/pracownik/1049/anna_herman-antosiewicz)
Section Board Member
Department of Medical Biology and Genetics, Faculty of Biology, University of Gdańsk, 80-308 Gdańsk, Poland
Interests: cancer chemoprevention and treatment; phytochemicals; signal transduction pathways; autophagy; cell death mechanisms

Dr. Eric Huang
Website (https://medicine.utah.edu/faculty/mddetail.php?facultyID=u0516990)
Section Board Member

Department of Neurosurgery, University of Utah, Salt Lake City, UT, USA
Interests: brain tumor; cancer biology/metabolism; tumor hypoxia; prognosis
Special Issues, Collections and Topics in MDPI journals

Dr. Miguel Idoate
Website (https://www.us.es/trabaja-en-la-us/directorio/miguel-angel-idoate-gastearena)
Section Board Member
Department of Pathology, School of Medicine, Virgen Macarena University Hospital, University of Seville, 41009 Seville, Spain
Interests: immunooncology; cancer; pathology; molecular pathology; gliomas; neuropathology; oncogenesis; breast cancer; biomarkers
Special Issues, Collections and Topics in MDPI journals

Dr. Jan Ježek
Website (https://sciprofiles.com/profile/jezek)
Section Board Member
1. The Wellcome Trust/Gurdon Cancer Research Institute, University of Cambridge, Cambridge CB2 1QN, UK
2. Department of Genetics, University of Cambridge, Cambridge CB2 1QN, UK
Interests: mitochondrial biology; mitochondrial metabolism; redox biology; bioenergetics; cancer research; tumor suppressors; mitochondrial stress signaling

Dr. Michalis Karamouzis
Website (https://www.esmo.org/about-esmo/profiles/michalis-karamouzis)
Section Board Member
Medical School, National and Kapodistrian University of Athens, Athens, Greece
Interests: upper GI tumors; lower GI tumors; GU tumors; head and neck carcinomas; translational research; immuno-oncology

Prof. Dr. Thomas Kietzmann
Website (https://www.oulu.fi/university/researcher/thomas-kietzmann)
Section Board Member
Faculty of Biochemistry and Molecular Medicine, Biocenter Oulu, University of Oulu, FI-90014 Oulu, Finland
Interests: hypoxia; hypoxia-inducible factor; reactive oxygen species; metabolism; growth factor and hormone signaling; kinases; cancer metabolism
Special Issues, Collections and Topics in MDPI journals

Dr. Hee-Je Kim
Website (https://www.cmcseoul.or.kr/page/en/doctor/189/D0001178)
Section Board Member
Division of Hematology, Department of Internal Medicine, Catholic Hematology Hospital, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea
Interests: transplantation medicine; molecular biology in leukemia; transplantation immunology; cancer immunotherapy; tumor microenvironment
Special Issues, Collections and Topics in MDPI journals

Dr. Yun-Hee Kim
Website (https://www.cmu.edu/nanotechnology-forum/Forum_16/CV/KOREA/Yun-Hee%20Kim_Bio.pdf)
Section Board Member
Cancer Biomedical Science, National Cancer Center Graduate School of Cancer Science and Policy, Goyang 10408, Republic of Korea
Interests: pancreatic cancer; cholangiocarcinoma; organoid; tumor microenvironment
Special Issues, Collections and Topics in MDPI journals

Dr. Evangelos Kolettas
Website (https://www.imbb.forth.gr/en/research-en/biomedical-research/item/5510-evangelos-kolettas)
Section Board Member
1. Laboratory of Biology, School of Medicine, Faculty of Health Sciences, University of Ioannina, Ioannina, Greece
2. Division of Biomedical Research, Institute of Molecular Biology and Biotechnology (IMBB), Foundation for Research and Technology (FORTH), Ioannina, Greece
Interests: cancer; senescence; DNA damage; inflammation; cell signalling; NF-kappaB; E2F; transcriptional regulation; epigenetics; epithelial-to-mesenchymal cell transition
Special Issues, Collections and Topics in MDPI journals

Dr. Jesus Lacal
Website (https://diarium.usal.es/jlacal/about-dr-lacal/?lang=en)
Section Board Member
Department of Microbiology and Genetics, Faculty of Biology, University of Salamanca, 37007 Salamanca, Spain
Interests: genetic variants and molecular mechanisms of rare diseases; RASopathies; cancer cell biology; genetics of intelligence; personalized precision medicine

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Prof. Dr. Nathalie Lassau
Website (https://www.gustaveroussy.fr/fr/nathalie-lassau)
Section Board Member
Institut Gustave Roussy, BioMaps, Inserm, CNRS, CEA, Université Paris-Saclay, Villejuif, France
Interests: functional imaging in oncology; biomarkers in oncology; DCE-US; elastography; radiomics; artificial intelligence on imaging

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Dr. Matteo Lazzeroni
Website (https://www.researchgate.net/profile/Matteo_Lazzeroni)
Section Board Member
Division of Cancer Prevention and Genetics, IEO, European Institute of Oncology, IRCCS, 20141 Milan, Italy
Interests: cancer prevention; presurgical / Window of Opportunity (WOP) trials; phytochemicals in cancer prevention; drug repurposing in cancer prevention; risk biomarkers; breast intraepithelial neoplasia management
Special Issues, Collections and Topics in MDPI journals

Dr. Dakeun Lee
Website (https://www.aminer.cn/profile/dakeun-lee/53f456d5dabfaeecd69ecb1e)
Section Board Member
Department of Pathology, Ajou University School of Medicine, Suwon 16499, Republic of Korea
Interests: cancer biology; tumor microenvironment; cancer-associated fibroblast; extracellular matrix; metastasis; organoid; pathology; gastric cancer; pancreas cancer; colon cancer; biliary cancer; biomarker; prognosis
Special Issues, Collections and Topics in MDPI journals

Dr. Hyuk Lee
Website (https://www.samsunghospital.com/gb/language/m_english/common/doctorProfile.do?dr_no=1480)
Section Board Member
Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea
Interests: gastric cancer; esophageal cancer; endoscopy

Dr. Jacqueline Lehmann-Che
Website (https://clicktime.symantec.com/3NDRMKvDAucUQ6RK4in6WrN6H2?u=https%3A%2F%2Funiv-paris-diderot.academia.edu%2FJacquelineLehmannChe)
Section Board Member
Molecular Oncology Unit, Department of Solid Tumor Genomics and INSERM U976, University of Paris, F-75010 Paris, France
Interests: molecular oncology; molecular biology; genetics; biochemistry; breast cancer; solid tumors

Dr. Ho Lin
Website (https://lifes.nchu.edu.tw/web/faculty/detail.php?lang=zh_tw&cid=1&id=13)
Section Board Member
Department of Life Sciences, National Chung Hsing University, Taichung 402204, Taiwan
Interests: cancer biology; cell biology; signal transduction; endocrinology
Special Issues, Collections and Topics in MDPI journals

Dr. Ming-Jung Liu
Website (https://orcid.org/0000-0002-2657-565X)
Section Board Member
1. Division of Gastroenterology, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan
2. Regenerative Medicine and Cell Therapy Research Center, Kaohsiung Medical University, Kaohsiung, Taiwan
Interests: cancer; signaling pathways
Special Issues, Collections and Topics in MDPI journals

Dr. Francesca Lovat
Website (https://www.researchgate.net/profile/Francesca_Lovat)
Section Board Member

Comprehensive Cancer Center, Ohio State University, Columbus, OH 43210, USA
Interests: tumors; cancer research; cell biology; cancer diagnostics; cancer genetics; molecular biology; mouse model
Special Issues, Collections and Topics in MDPI journals

Dr. Francesca Magherini
Website (https://www.unifi.it/p-doc2-2016-0-A-2b333c293328-0.html)
Section Board Member
Department of Experimental and Clinical Biomedical Sciences “Mario Serio”, Universita degli Studi di Firenze, Florence, Italy
Interests: gold-based anticancer drugs; auranofin; thioredoxin reductase; ovarian cancer; cancer cell metabolism; proteomics; redox proteomics
Special Issues, Collections and Topics in MDPI journals

Dr. Carlos Martínez-Campa
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Department of Physiology and Pharmacology, University of Cantabria, Santander, Spain
Interests: melatonin; breast cancer; chemotherapy; radiotherapy; apoptosis; angiogenesis; gene expression
Special Issues, Collections and Topics in MDPI journals

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Section Board Member
Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Via G. Campi 287, 41125 Modena, Italy
Interests: thymidylate synthase; thymidylate synthase inhibitors; ovarian cancer cells; platinum drug resistance; anticancer drug-resistance; DNA intercalators; anticancer drug combinations; bipyridyl-Pt(II)-Pd(II)-thiourea complexes; phenanthroline-Pt(II)- Pd(II)-thiourea complexes

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Website (https://www.walshmedicalmedia.com/editor/gianluigi-ubaldo-mazzoccoli-7179)
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Department of Medical Sciences, Division of Internal Medicine and Chronobiology Laboratory, Fondazione IRCCS Casa Sollievo della Sofferenza, 71013 San Giovanni Rotondo, Italy
Interests: chronobiology; chronogenetics; metabolism; autophagy; oxidative stress; inflammation; aging
Special Issues, Collections and Topics in MDPI journals

Prof. Dr. Amichay Meirovitz
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Section Board Member
The Legacy Heritage Center & Dr. Larry Norton Institute, Soroka Medical Center, Ben Gurion University, Beer Sheva 84105, Israel
Interests: radioresistance; radiosensitivity; radiotherapy; targeted therapy

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Website (http://cvscience.aviesan.fr/cv/311/olivier-micheau)
Section Board Member
INSERM UMR1231, Lipides Nutrition Cancer, UFR Sciences de Santé, UBFC, Université Bourgogne Franche-Comté, Dijon, France
Interests: apoptosis; TNF; TRAIL; signaling; cancer
Special Issues, Collections and Topics in MDPI journals

Dr. Massimo Moro
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Section Board Member
Tumor Genomics Unit, Department of Research, Fondazione IRCCS Istituto Nazionale dei Tumori, 20133 Milan, Italy
Interests: lung cancer; patient-derived xenografts; metabolism; LKB1; KRAS; miRNA; metformin; fast-mimicking diet; immune checkpoint inhibition
Special Issues, Collections and Topics in MDPI journals

Prof. Dr. Luciano Mutti
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Section Board Member
Department of Biology, College of Science and Technology, Temple University, Philadelphia, PA 19122, USA
Interests: translational vancer research; thoracic oncology; mesothelioma
Special Issues, Collections and Topics in MDPI journals

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Website (https://www.researchgate.net/profile/Yasuhiro-Nakamura-2)
Section Board Member
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Interests: pathology of endocrine and urological disorders
Special Issues, Collections and Topics in MDPI journals

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Website (https://www.researchgate.net/profile/Karim-Nayernia-2)
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European Center for Personalized Medicine, Düsseldorf, Germany
Interests: metastatic cancer; resistance

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Website (https://www.istitutotumori.na.it/old/IstitutoPascale/CCVV_CC/CV_CC_Ricerca/CV_PalmaGiuseppe.pdf)
Section Board Member
SSD Animal Unit, Istituto Nazionale Tumori-IRCCS-Fondazione "G. Pascale", 80131 Naples, Italy
Interests: microbiota; oncology; pharmacology; in vivo experiment; preclinical experiment; nutrition

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2. Faculté de Pharmacie, 4 Avenue de l'Observatoire, 75006 Paris, France
Interests: interface between signal transduction and cancer with a focus on the alternative NF-kappaB signaling pathway, how it is regulated, and its contributions towards tumor development and resistance to conventional cancer therapies
* Section: Cancer Biology and Oncology
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Interests: gynecological cancers; diagnosis; prognosis; miRNA; gene expression

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Editorial Board Member

1. Department of Human Development Nutrition Program, School of Public Health, University of Puerto Rico Medical Sciences Campus, P.O. Box 365067, San Juan, PR 00936-5067, USA
2. Medical Sciences Campus, School of Public Health, University of Puerto Rico, San Juan, PR 00936, USA
3. School of Chiropractic, Universidad Central del Caribe, Bayamon, PR 00960, USA

Interests: cancer biology; nutrition; cancer; biochemistry; public health; metabolism; nutritional education; hu nutrition; nutrition assessment; nutritional and metabolic diseases

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Dr. Jörg-Andrew Westhoff

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Editorial Board Member

Department of Pediatrics and Adolescent Medicine, Ulm University Medical Center, 89081 Ulm, Germany

Interests: glioblastoma; combination therapy; apoptosis; temozolomide

Special Issues, Collections and Topics in MDPI journals

Dr. Yoshihiro Abiko

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Section Board Member

Division of Oral Medicine and Pathology, Department of Human Biology and Pathophysiology, School of Dentistry, Health Sciences University of Hokkaido, 1757 Kanazawa, Ishikari-Tobetsu, Hokkaido 061-0293, Japan

Interests: epigenetics; DNA methylation; oral cancer; epithelial antimicrobial peptides; oral mucosa; oral microbe; anti-aging

Dr. Agusti Alentorn

Website (https://www.aphp.fr/offre-de-soin/medecin/4069140/066/23)

Section Board Member

Department of Neurology 2, Groupe Hospitalier Pitié Salpêtrière, AP-HP, Paris, France

Interests: neuro-oncology; brain tumors; cancer genomics; primary central nervous system lymphoma; bioinformatics

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Dr. Mohammed A. Aleskandarany

Website (https://www.derby.ac.uk/staff/mohammed-aleskandarany/)

Section Board Member

University of Department of Biomedical and Forensic Science, University Derby, Derby DE22 1GB, UK

Interests: translational cancer research for developing prognostic and predictive tools to improve cancer patients' outcome—this is through refining the currently used prognostic and predictive parameters and mining for novel ones for accurate patients' risk stratification and personalised management

Dr. [illegible] J. Allison
Website (https://pure.hud.ac.uk/en/persons/sj-allison)
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School of Applied Sciences, University of Huddersfield, Huddersfield HD1 3DH, UK
Interests: cancer metabolism; NAD^+ biology; sirtuins; cancer selectivity; novel targets; target deconvolution
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Dr. Michele Ammendola
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Department of Health Science, Digestive Surgery Unit, Medical School, University “Magna Graecia”, Viale Europa, Germaneto, 88100 Catanzaro, Italy
Interests: surgical oncology; angiogenesis and lymphangiogenesis in gastrointestinal tumor; molecular aspects; traslational reserch in surgery
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[illegible]lia Azzariti
[illegible]te (https://www.sanita.puglia.it/web/irccs/direttori/-/document_library_display/9RCzjmFcJOEE/view/7985966)
Section Board Member
Laboratory of Experimental Pharmacology, IRCCS Istituto Tumori Giovanni Paolo II, V.le O. Flacco, 65, 70124 Bari, Italy
Interests: cancer cells apoptosis; cancer therapy; cancer diagnostics; gemcitabine/nabpaclitaxel in pancreatic cancer; cancer research; cancer biomarkers; cell cycle regulation; signal transduction; phosphorylation; cell migration

Prof. Dr. Bo-Ying Bao
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Section Board Member
Department of Pharmacy, China Medical University, Taichung 406, Taiwan
Interests: cancer; molecular epidemiology; prognosis; biomarker; prostate

[illegible] Belyaev
[illegible]te (https://www.sav.sk/?lang=en&doc=user-org-user&user_no=6474)
Section Board Member
Cancer Research Institute, Biomedical Research Center, Slovak Academy of Sciences, Dúbravska cesta 9, 845 05 Bratislava, Slovakia
Interests: DNA damage and repair; apoptosis; stem cells; ionizing and non-ionizing radiation; electromagnetic fields
Special Issues, Collections and Topics in MDPI journals

[illegible]r. Antonio Biondi
[illegible]ps://recognition.webofscience.com/awards/highly-cited/2021/) Website (http://www.chirmed.unict.it/docenti/antonio.giuseppe.biondi)
Section Board Member

Department of General Surgery and Surgical—Medical Specialties, University of Catania, Catania, Italy
Interests: colorectal cancer; general surgery; screening; biomarkers; quality of life; liquid biopsy; microbiota
Special Issues, Collections and Topics in MDPI journals

Dr. Chiara Brignole
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Section Board Member
Area Aggregazione Laboratori Ricerca, U.O.S.D. Laboratorio Terapie Sperimentali in Oncologia, IRCCS Istituto Giannina Gaslini, 16147 Genoa, Italy
Interests: neuroblastoma; targeted therapy; liposomes; precision medicine for cancer; tumor microenvironment; macrophages and cancer
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Dr. Wen-Wei Chang
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Department of Biomedical Sciences, Chung Shan Medical University, Taichung 40201, Taiwan
Interests: cancer stem cells; cancer immunology; signal transduction; extracellular vesicles; probiotics; drug discovery

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Section Board Member
Department of Pathology, School of Medicine, College of Medicine, Taipei Medical University, Taipei 110, Taiwan
Interests: inflammation; cell movement; colonic neoplasms

Dr. Yongheng Chen
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Xiangya Hospital, Central South University, Changsha, China
Interests: cancer; structural biology; drug development

Dr. Chih-Yen Chien
Website (https://cgmmrc.cgu.edu.tw/p/406-1029-71391,r1825.php?Lang=en)
Section Board Member
1. Department of Otolaryngology, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan
2. College of Medicine, Chang Gung University, Taoyuan City, Taiwan
Interests: HNSCC; nasopharyngeal carcinoma; oropharyngeal cancer; oral cancer; laryngeal cancer
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Dr. Jae-Hoon Chung
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Department of Urology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul 06351, Republic of Korea
Interests: prostate cancer; kidney cancer; urothelial carcinoma; genitourinary oncology

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Section Board Member
Humanitas Gavazzeni, Oncol Unit, Bergamo, Italy
Interests: Lymphoma

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Department of Genetics, LSU Health Sciences Center, New Orleans, LA, USA
Interests: breast cancer; neuroendocrine tumors; notch signaling; stem cells

Prof. Dr. Marina De Rosa
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1. Department of Molecular Medicine and Medical Biotechnology, University of Naples Federico II, 80131 Naples, Italy
2. Ceinge Biotecnologie Avanzate, 80131 Naples, Italy
Interests: hereditary colorectal cancer; gastrointestinal polyposis syndromes; sporadic colorectal cancer; epithelial to mesenchymal transition; cancer stem cell; molecular diagnosis; precision medicines; cancer resistance to therapy
Special Issues, Collections and Topics in MDPI journals

Prof. Dr. Silvia Di Agostino
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Oncogenomic and Epigenetic Unit, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Regina Elena National Cancer Institute, 00144 Rome, Italy
Interests: genomic instability; cell cycle checkpoints; DNA repair; transcriptional regulation; molecular oncology; head and neck; p53 family; mutant p53; Hippo pathway
Special Issues, Collections and Topics in MDPI journals

Prof. Dr. Qiongzhu Dong
Website (https://orcid.org/0000-0002-2433-7199)
Section Board Member
Key Laboratory of Whole-Period Monitoring and Precise Intervention of Digestive Cancer, Shanghai Municipal Health Commission (SMHC), Minhang Hospital, Fudan University, Shanghai 201199, China
Interests: cancer research; cancer biomarkers; cancer therapy; tumor metabolism; tumor immunology
Special Issues, Collections and Topics in MDPI journals

Prof. Dr. Randolph C. Elble
Website (http://www.siumed.edu/pharm/faculty/randolph-elble.html)
Section Board Member
Department of Pharmacology, Southern Illinois University School of Medicine, Springfield, IL 62794, USA
Interests: epithelial differentiation processes in breast, oral, and lung cancers; metastasis mechanisms; cell junctional signaling; EGFR, Her2, and E-cadherin in anoikis; role of intracellular calcium stores in proliferation,

differentiation, and cell death; p53, cell stress, and DNA damage response; cell senescence; CLCA gene family

Special Issues, Collections and Topics in MDPI journals

Dr. Alfio Ferlito

Website (http://www.ihnsg.com/)

Section Board Member

Coordinator of the International Head and Neck Scientific Group, Padua, Italy

Interests: head and neck cancer; neuroendocrine carcinoma

Dr. David J. FitzGerald

Website (https://ccr.cancer.gov/Laboratory-of-Molecular-Biology/david-j-fitzgerald)

Section Board Member

Center for Cancer Research, National Cancer Institute, Bethesda, MD, USA

Interests: cancer; monoclonal antibodies; bacterial toxins; immunotoxins; tumor microenvironment and apoptosis

Dimitrios Gyftopoulos

Website (https://www.webmedcentral.com/wmc_editor_details/3588)

Section Board Member

Department of Anatomy, University of Patras School of Medicine, Rion, 26504 Patras, Greece

Interests: prostate cancer; metastasis; EMT

Dr. Yazhou He

Website (https://wcsph.scu.edu.cn/info/1257/9608.htm)

Section Board Member

Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, Edinburgh, UK

Interests: genetic and molecular epidemiology on cancer with a particular interest in colorectal cancer

Special Issues, Collections and Topics in MDPI journals

Dr. Khalil Helou

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Section Board Member

Department of Oncology, Sahlgrenska University Hospital, 405 30 Gothenburg, Sweden

Interests: cancer; breast and ovarian cancer; microarray; gene expression; DNA copy alterations; TMA; cell transfection; patient derived xenografts; biomarkers

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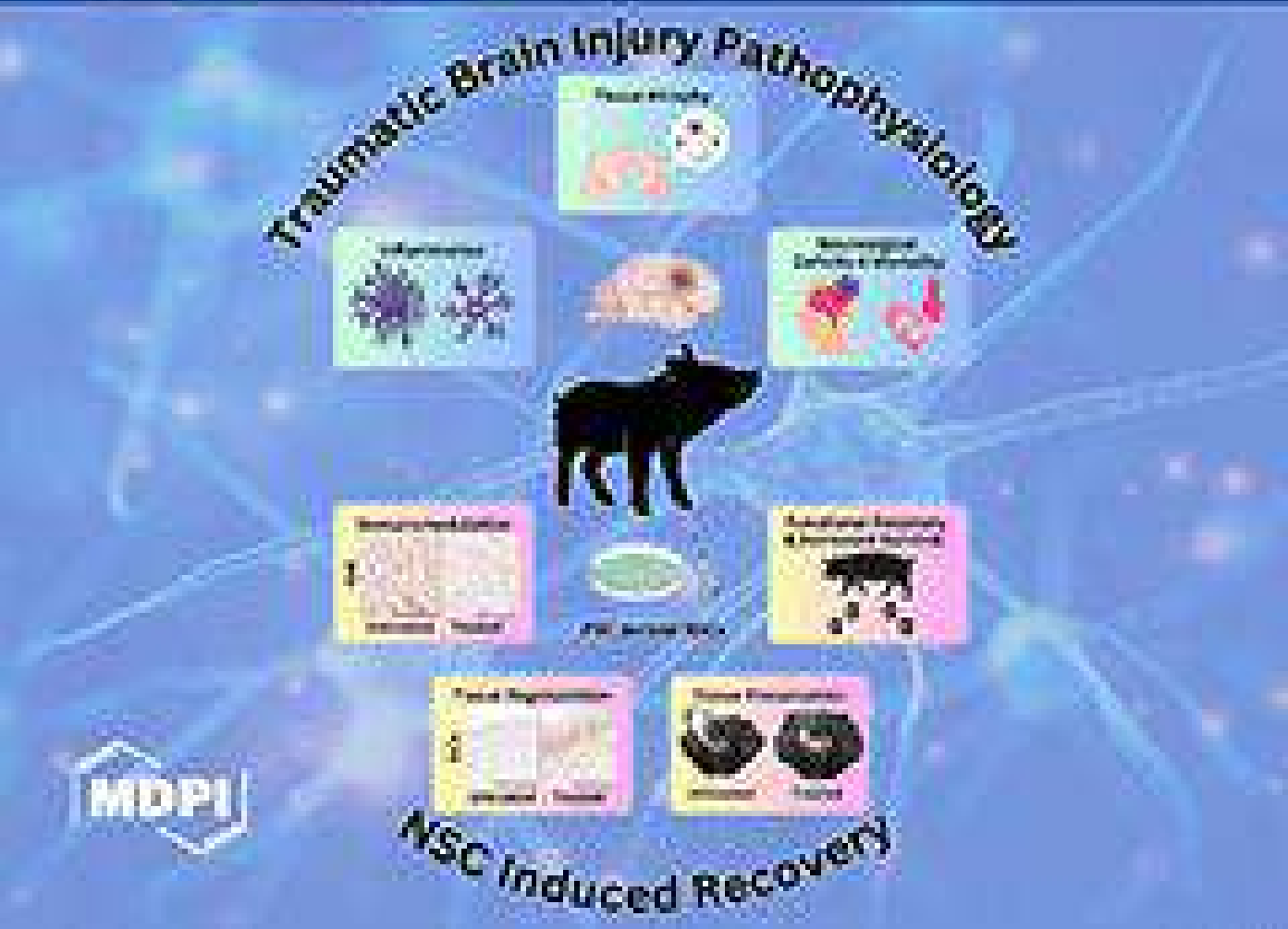

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Abstract: Background: In Indonesia, cultural practices such as betel quid chewing, smoking, and alcohol consumption are prevalent. These practices are known risk factors for oral cancer and may influence the salivary profile, which is essential for maintaining oral health. Purpose: To compare the salivary profiles of individuals with and without risk factors for oral cancer. Methods: The study included 49 individuals identified as having risk factors for oral cancer. Unstimulated saliva samples were collected. Various parameters were measured, including salivary pH, flow rate (FR), thickness, color, turbidity, and the levels of IL-1β and IL-8. Data were analyzed using Chi-square and *t*-tests. Results: A significant difference was found in salivary IL-1β levels between the two groups ($p = 0.009$), with higher levels observed in individuals with oral cancer risk factors. Notably, the salivary IL-1β concentrations showed significant differences between the smoking group ($p = 0.021$; OR = 2.94) and the alcohol-drinking group ($p = 0.007$; OR = 4.96) compared to the control group. However, no significant differences were observed between the groups in terms of salivary viscosity, color, turbidity, flow rate, acidity, or IL-8 levels ($p > 0.05$). Conclusion: Individuals with risk factors for oral cancer exhibit distinct salivary IL-1β profiles compared to those without such risk factors, particularly those who practice alcohol drinking.

Keywords: risk factor; saliva; oral cancer

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1. Introduction

The World Health Organization (WHO) estimates that around 58% of global oral and oropharyngeal cancer cases occur in South and Southeast Asia, including Indonesia [1]. Various risk factors contribute to the development of oral cancer, including tobacco smoking, alcohol consumption, chronic inflammation, human papillomavirus (HPV), genetic predisposition, and dietary habits [2,3].

Each province in Indonesia has its distinct traditions and cultures. The practice of chewing betel quid, a tradition passed down through generations, is prevalent. In 2004, the International Agency for Research on Cancer (IARC) classified betel quid chewing, with or without tobacco, as carcinogenic to humans [4]. The consumption of alcoholic beverages, particularly a traditional alcohol known as "moke" or "sopi" derived from palm tree sap with a high ethanol content, is another prevalent habit among the Flores population [5]. According to the 2018 Indonesian National Health Survey, smoking prevalence in Indonesia is significant, with East Nusa Tenggara having notably high rates of 19% and non-routine smokers at 7.3%. It is also the second-highest province with a proportion of the consumption of alcoholic beverages in the past month of 15.6%. Tobacco exposure, a component of smoking, is a significant risk factor for oral cancer [6].

Saliva plays a crucial role in maintaining oral health through various functions and properties. It acts as a lubricant, aiding in chewing, swallowing, and speaking, while forming a protective barrier against mechanical damage and pathogens [7]. Saliva, as a bodily fluid, reflects various physiological and pathological conditions. It is easily accessible, cost-effective, and non-invasive, making it an ideal medium for diagnostic purposes [8,9]. Saliva has a buffering capacity that neutralizes acids produced by bacteria, preventing tooth enamel demineralization and promoting remineralization. Its antimicrobial agents, such as lysozyme and lactoferrin, control the growth of oral microbiota and prevent infections [10]. It also acts as a solvent for taste substances, facilitating interaction with taste receptors and maintaining taste buds [11]. Saliva is primarily composed of water (99%) along with electrolytes, mucus, antibacterial compounds, and enzymes. Its viscosity, influenced by mucin glycoproteins, is essential for its lubricating function [12]. Salivary flow rate varies with factors like hydration and diet, with a normal unstimulated flow at 0.3–0.4 mL/min and stimulated flow at 1–2 mL/min [13]. The pH of saliva ranges from 6.2 to 7.6, maintained by bicarbonate, phosphate, and protein systems, contributing to its buffering capacity [14]. In the presence of a tumor, the pH of saliva becomes acidic. This change is due to the anaerobic metabolism of glucose under the hypoxic conditions created by the tumor. The acidic environment provides a supportive setting for a tumor cell to survive and proliferate [15]. Saliva contains proteins, including cytokines, which have been identified as potential biomarkers for various diseases, including oral cancer. IL-8 and IL-1β, cytokines implicated in processes such as replication, angiogenesis, and tumor development, are particularly relevant in oral cancer diagnosis [15–17]. Several studies have indicated that salivary cytokines may serve as diagnostic biomarkers for various diseases, including oral cancer. Pro-inflammatory cytokines such as IL-1β, IL-6, IL-8, INF-γ, and TNF-α are known to enhance cell growth, disrupt tumor suppression mechanisms, and impair host immunity, leading to cancer progression. Hence, over 100 potential biomarkers for detecting oral cancer have been observed, with IL-8 and IL-1β playing crucial roles in cell replication, angiogenesis, cell adhesion, and tumor development. Several studies have detected IL-1β and IL-8 in the serum and saliva (IL-1β 0.5–12 pg/mL; IL-8 < 62 pg/mL) of patients with oral squamous cell carcinoma (OSCC), highlighting their significance as biomarkers for oral cancer [18,19]. Studies have shown their presence in the serum and saliva of patients with OSCC, underscoring their significance as biomarkers [20].

Given the prevalence of oral cancer risk habits in communities like betel nut chewing, alcohol consumption, and smoking, it is hypothesized that these practices may influence salivary profiles, impacting oral health. However, research on the salivary profile within these communities, especially in Flores, East Nusa Tenggara, where such cultural practices are prominent, remains scarce. Hence, this study aimed to assess the salivary profile of individuals with and without oral cancer risk habits in this context.

2. Materials and Methods

This observational cross-sectional study involved 77 subjects, comprising 49 individuals with identified risk habits and 28 without such habits, conducted on Flores Island, East Nusa Tenggara province. The determination of the sample size was based on parameters derived from previous studies, specifically an effect size of 1.72 as reported by Amtha et al. (2015), with a study power of 95% and a significance level (α) set at 0.05, calculated using G*Power 3.1.9.7 software [5].

Inclusion criteria encompassed individuals with a history of betel nut chewing, alcohol consumption, and/or smoking for a minimum duration of 1 year. Conversely, exclusion criteria were applied to subjects currently taking antibiotics, antihistamines, or long-term steroids, undergoing cancer treatment, or presenting with cancerous lesions in other organs. All participants provided informed consent before data collection commenced. Ethical approval for the study was obtained from the Ethics Commission of the Faculty of Dentistry, University of Trisakti, under reference number 022/S3/KEPK/FKG/7/2022.

2.1. Collection of Unstimulated Salivary Samples

Saliva collection procedures were conducted in the morning, with subjects instructed to refrain from eating, drinking, smoking, or chewing betel quid for a period of 60 min prior to collection. The saliva collection method employed was the spitting technique, where participants were instructed to expectorate saliva into a falcon tube for a duration of 10 min.

2.2. Assessment of the Color, Turbidity, Viscosity, and pH of Saliva

The assessment of color and turbidity was conducted through visual inspection by two calibrated oral medicine specialists. Salivary acidity levels were measured using a digital pH meter (Mediatech pH Meter Digital Automatic Calibration P-2Z), which was calibrated beforehand using 6.86 and 4.00 buffers.

2.3. Examination of IL-1β and IL-8 Levels Using an Enzyme-Linked Immunosorbent Assay (ELISA)

Salivary protein separation was conducted using the Genezol Kit (Geneaid, Cat# GZR200). The process involved sample homogenization, followed by the separation of RNA, DNA, and protein in saliva samples. Protein extraction, deposition, washing, and resuspension were then performed to obtain the protein fraction.

Subsequently, the levels of IL-1β and IL-8 (expressed in pg/mL) in saliva were determined utilizing the ELISA method. For this purpose, primers and technical materials specific to IL-1β and IL-8 were utilized (Bioassay Technology Laboratories, Cat# E0143HU, E0089HU). Sample testing was conducted in duplicate to ensure accuracy and reliability.

The optical density values in each well were measured using a microplate reader set to a wavelength of 450 nm. This facilitated the quantification of IL-1β and IL-8 levels in the saliva samples, providing valuable insights into their concentrations.

2.4. Data Analysis

Bivariate analysis was conducted using the Chi-square test for non-parametric data and the *t*-test for normally distributed data. A significance level of $p < 0.05$ was deemed statistically significant in determining differences between groups. Odds ratios were calculated to assess the significance of cytokine levels between the groups, providing further insight into the associations observed. Additionally, Kaplan–Meier analysis was used to determine the interleukin level.

3. Results

3.1. Subject Characteristics

Table 1 shows significant differences in risk factors based on gender ($p = 0.007$). Both males (93.33%) and females (56.4%) exhibited a higher prevalence of risk factors compared to those without such factors. Males primarily presented with smoking and alcohol consumption habits (18.37%), while females predominantly engaged in drinking alcohol and betel quid chewing (38.78%). Additionally, there was a notable disparity in risk factors across age groups ($p = 0.035$), with individuals over 35 demonstrating a higher propensity for risk factors compared to those under 35. Among the 77 study participants, no significant differences were observed in salivary viscosity ($p = 0.459$), color ($p = 0.476$), turbidity ($p = 1.000$), and salivary flow rate ($p = 0.235$) between subjects with and without risk factors.

In this study, the simultaneous consumption of alcohol and betel quid accounts for 38.77% of the population. Additionally, betel quid chewing alone is prevalent (24.48%) in the population. Filter cigarettes are the predominant type of tobacco product used in the region. The preferred alcoholic beverage among community members is “moke putih or tua bhara”. The common composition of betel quid typically includes a mixture of inflorescence betel leaves, unripe areca nut, and lime.

Table 1. Population characteristics.

Variable	Risk Factor		Non-Risk Factors		Total	*p*-Values
	n	%	n	%	n	
Gender						
Male	14	93.33	1	6.67	15	0.008 **
Female	35	56.45	27	43.55	62	
Age (years)						
<35.3	12	46.15	14	53.85	26	0.035 *
>35.3–42.7	16	64	9	36	25	
>42.7	21	80.77	5	19.23	26	
Salivary viscosity						
Dilute	30	60	20	40	50	0.459
Thick	19	70.37	8	29.63	27	
Color						
Colorless	29	60.42	19	39.58	48	0.476
Colored	20	68.97	9	31.03	29	
Turbidity						
Clear	8	61.54	5	38.46	13	1.000
Cloudy	41	64.06	23	35.94	64	
Salivary flow rate (mL/10 min)						
<3.2	20	55.55	16	44.44	36	0.235
>3.2	29	70.73	12	29.27	41	
Risk factor habit						
Smoking (S)	1	2.04	-	-	1	
Alcohol drinking (A)	5	10.2	-	-	5	
BQ Chewing (BQ)	12	24.48	-	-	12	
S + A	10	20.40	-	-	10	
S + BQ	1	2.04	-	-	1	
A + BQ	19	38.77	-	-	19	
S + A + BQ	1	2.04	-	-	1	
BQ Chewing composition						
Betel leaf, areca nut, lime	16	100	-	-	16	
Betel leaf, areca nut, lime, tobacco	1	100	-	-	1	
Betel fruit, areca nut, lime	2	100	-	-	2	
Betel fruit, betel leaf, areca nut, lime	13	100	-	-	13	
Betel fruit, betel leaf, areca nut, lime, gambier, tobacco	1	100	-	-	1	

S, smoking; A, alcohol drinking; BQ, betel quid; * $p < 0.01$; ** $p < 0.05$.

3.2. pH, Salivary Flow Rates, and Interleukin Level between Risk Factor Groups

Figure 1 showed the disparities among community cohorts, categorized by the presence or absence of risk factors for oral cancer. Notably, a substantial difference was found in the salivary IL-1β profile between these cohorts, where individuals with identified risk factors exhibit markedly elevated IL-1β levels. Subsequent examination discloses noteworthy variations in IL-1β concentrations between smokers and non-smokers, as smokers demonstrate notably augmented IL-1β levels compared to their non-smoking counterparts. Similarly, a conspicuous distinction emerges in IL-1β concentrations between alcohol consumers and non-consumers, as the former exhibit higher IL-1β levels. Conversely, IL-8 levels do not manifest significant disparities across the cohorts.

Figure 2 describes that IL-1β levels may increase with prolonged use of tobacco, alcohol, and betel quid. Kaplan–Meier analysis showed that the mean estimated time for elevated IL-1β levels was 27.90 months (22.47–33.34). Notably, alcohol consumption appears to accelerate the increase in IL-1β levels more rapidly compared to other oral cancer risk factors.

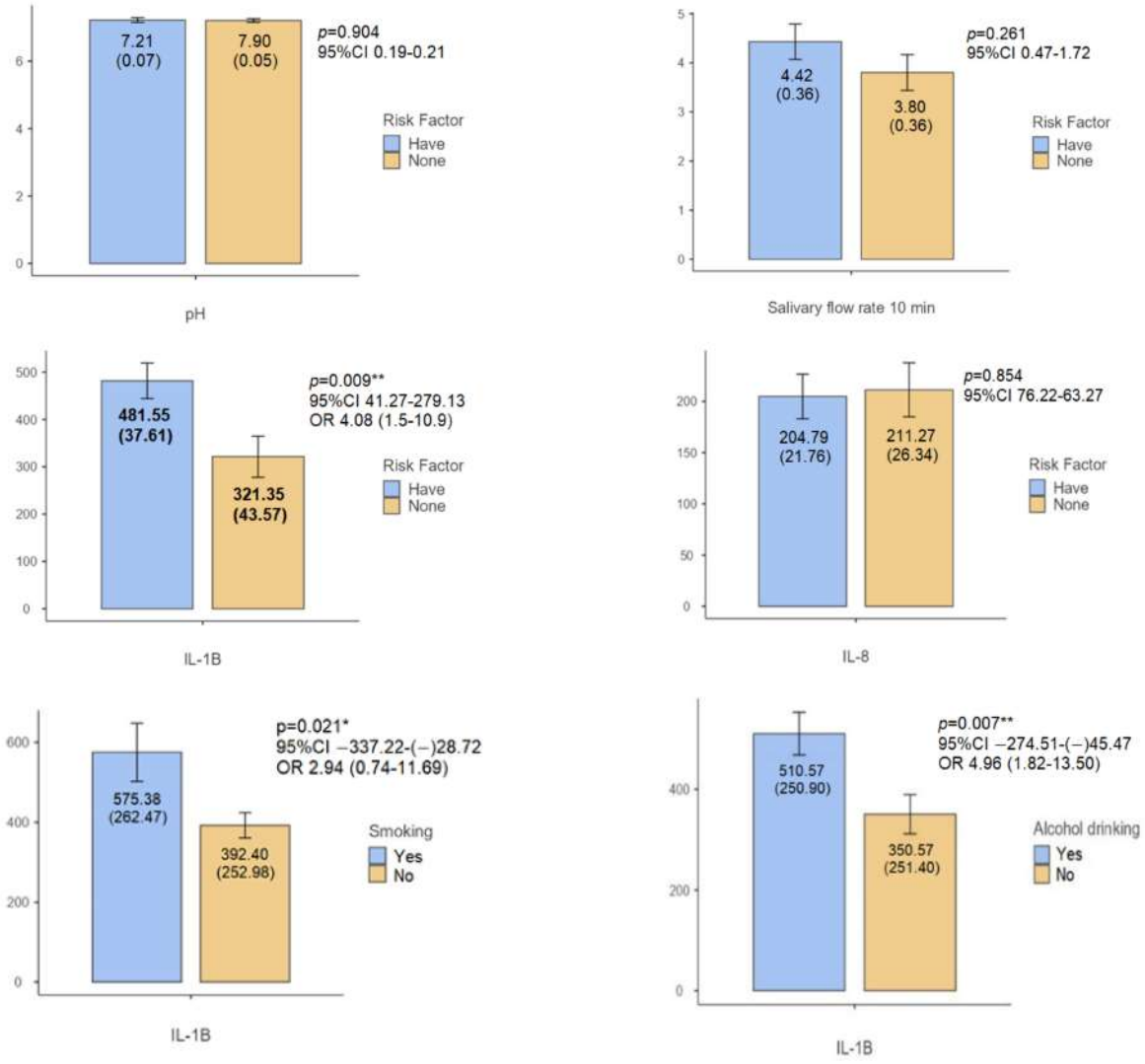

Figure 1. Bar chart showing the mean and standard deviation of pH, salivary flow rate, IL-1β, IL-8 among the studied groups. ** $p < 0.01$ * $p < 0.05$.

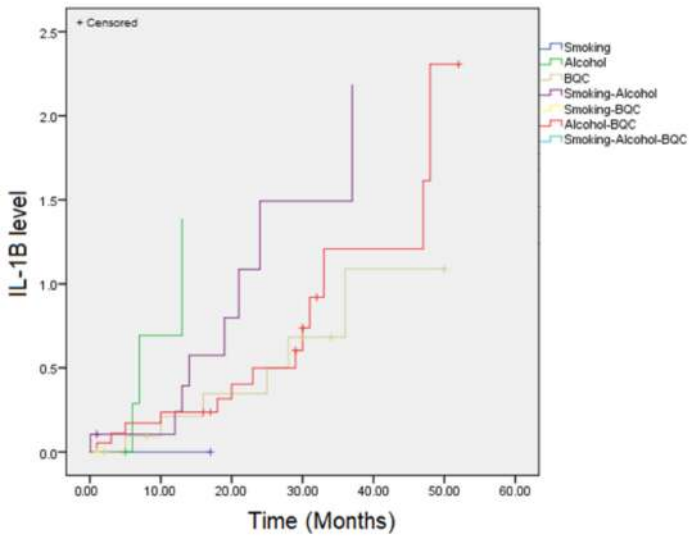

Figure 2. Kaplan–Meier analysis of time to IL-1β level among the groups.

3.3. Correlation between Duration of Risk Factor Habit and Salivary Viscosity

Table 2 shows the absence of a correlation between salivary viscosity and the duration of exposure to risk factors, including smoking, alcohol consumption, or betel nut chewing.

Table 2. Salivary viscosity and duration of risk factor habit.

Variable	Duration (Year)					
	Smoking		Alcohol Drinking		Betel Quid Chewing	
	Mean (SD)	*p*	Mean (SD)	*p*	Mean (SD)	*p*
Salivary viscosity		0.22		0.151		0.526
Dilute	22.94 (11.91)		16.60 (12.92)		17.42 (11.25)	
Thick	29.73 (18.28)		24.84 (19.30)		23.80 (22.26)	
Duration habit	20.08 (16.12)		19.85 (15.98)		25.79 (15.02)	

3.4. Comparison of Duration of Risk Factor Habit and Salivary Flow Rate

Table 2 shows that betel nut chewing has been the longest-standing risk factor among the study population, with an average duration of 25.79 years. However, the duration of habits such as smoking, alcohol consumption, and betel nut chewing did not significantly impact the salivary flow rate ($p > 0.05$) (Figure 3). In Figure 4, subjects with a habit of betel nut chewing demonstrate the highest salivary flow rate, followed by those who combine alcohol consumption with betel nut chewing.

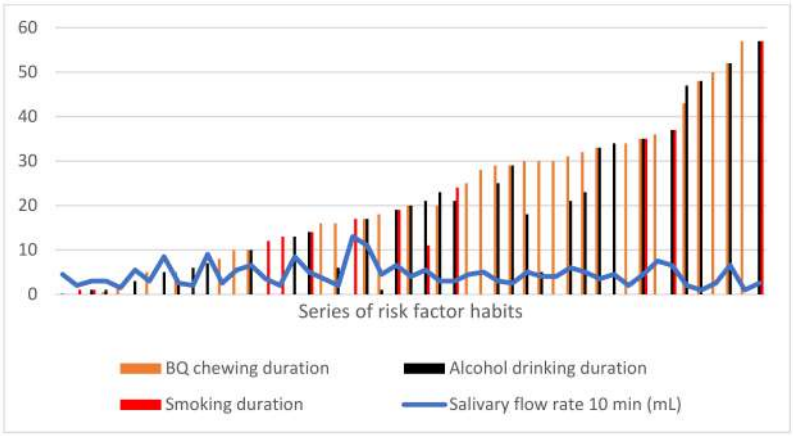

Figure 3. Series of risk factor habits based on the duration and salivary flow rate 10 min. (BQC, betel quid chewing).

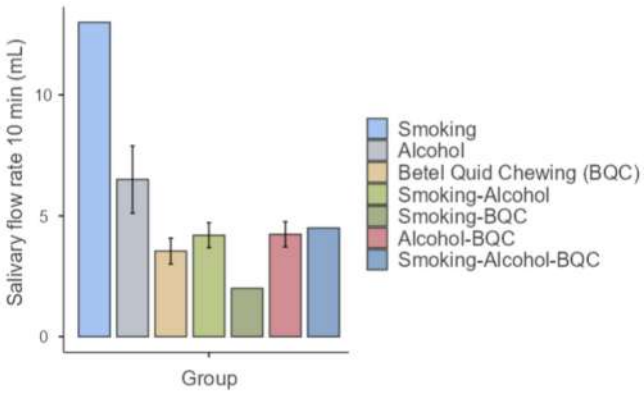

Figure 4. The salivary flow rates over a 10 min period vary across different risk factor habit groups as follows: smoking: 13.0 mL; alcohol: 6.50 (3.10) mL; betel quid chewing (BQC): 3.54 (1.86) mL; smoking–alcohol: 4.20 (1.64) mL; smoking–BQC: 2 mL; alcohol–BQC: 4.24 (2.28) mL; smoking–alcohol–BQC: 4.50 mL.

4. Discussion

Based on gender, the proportion of individuals with risk factors exceeded those without risk factors, 63.64% and 36.36%, respectively (Table 1). The most prevalent risk factor among males is the combined use of alcohol and smoking, consistent with data from the Indonesian Health National Survey indicating a higher prevalence of male smokers (47.3%) compared to females (1.2%) among individuals aged ≥10 years. Conversely, females predominantly engage in the combined consumption of alcohol and betel quid. According to a study by Amtha et al., locals perceive chewing betel leaves as invigorating and fatigue-reducing [5]. Both genders in the Bajawa region exhibit a significant inclination towards alcohol consumption, often attributed to the cold climate, which prompts locals to use alcohol for warmth [5]. Additionally, locals are known for producing homemade alcohol, referred to as "moke", commonly consumed during traditional ceremonies.

This study showed that individuals aged over 35 exhibit a higher prevalence of risk factors compared to those under 35 (Table 1). In a result consistent with the research conducted by Amtha R et al., a significant proportion of betel quid chewers and alcohol drinkers are elderly individuals [5]. Moreover, data from the Global Adult Tobacco Survey (GATS) 2021 indicates that smoking in the Indonesian population is most prevalent among individuals aged 25 to 44.

In this study, no significant difference was observed in the viscosity of saliva between participants with and without oral cancer risk factors (Figure 1 and Table 2). This lack of disparity can be attributed to the distinct effects of smoking, alcohol consumption, and betel quid chewing on salivary viscosity. Chronic alcohol consumption, as noted by Bronislaw L, leads to increased TNF expression and acinar cell apoptosis, potentially diminishing salivary function and production, consequently elevating saliva viscosity [21]. Studies by Nigar et al. and Petrušić et al. have indicated that smokers typically exhibit thicker saliva compared to non-smokers, potentially as a compensatory mechanism by salivary glands against the continuous deposition of toxins from cigarette compounds [22,23]. Conversely, research by Reddy et al. suggests that prolonged betel quid chewing may lead to a more watery salivation, possibly due to lower levels of potassium and amylase in the saliva of betel nut chewers [24]. In individuals with risk factors, there is no correlation observed between the duration of smoking ($p = 0.22$), alcohol consumption ($p = 0.151$), betel quid chewing ($p = 0.526$), and salivary viscosity (Figure 3). Notably, betel quid chewing poses the second-highest risk factor, resulting in a tendency for saliva viscosity to resemble that of the majority of patients without risk factors.

According to Anand et al., the habit of chewing betel quid often results in the production of blood-red saliva, with the stain becoming ingrained in the teeth, gums, and oral mucosa over time [25]. In the present study, no significant difference in saliva color was observed between patients with risk factors for oral cancer and those without ($p = 0.476$) (Table 1). This lack of distinction may be attributed to the study participants, the majority of whom exhibited high-risk behaviors such as alcohol consumption and betel quid chewing. The presence of high levels of ethanol in saliva due to alcohol consumption can have a solubilizing effect, leading to oral mucosa dryness. Consequently, the color of betel quid constituents may be dissolved, resulting in a lack of discernible differences between patients with and without risk factors.

Areca nut, a key component of betel quid, contains tannin, as identified by Horne et al. [26]. High salivary protein levels, induced by areca nut consumption, can lead to turbidity in saliva. Furthermore, the interaction between tannins and proteins forms a precipitate, resulting in astringency and haze development [26,27]. The study reported both patients with and without risk factors demonstrated a relatively high salivary flow rate, potentially increasing saliva's protein content and causing cloudiness. Subjects with risk factors also exhibited cloudy saliva, possibly due to lime present in the betel nut. Conversely, in the group without risk factors, turbidity may have been influenced by the limited saliva collection time of 10 min, during which participants typically expectorate saliva, leading to subconscious mucoid engagement and increased salivary turbidity.

In this study, no significant difference was found in the salivary flow rates between individuals with and without oral cancer risk factors (p = 0.235) (Table 1 and Figure 4). Notably, subjects with a singular habit of betel quid chewing exhibited the highest salivary flow rate, consistent with findings by Rooban et al., who reported that betel quid chewers had greater salivary flow rates compared to non-chewers [28]. This phenomenon is attributed to the enlargement of salivary glands resulting from persistent betel quid chewing, leading to an elevated salivary flow rate [28]. Contrary to the above, chronic alcoholics are prone to experiencing dry mouth, as suggested by Innenaga et al. The accumulation of ethanol and acetaldehyde can induce apoptosis and cell death in acinar cells, while alcohol intake may also lead to fat accumulation in salivary glands, acinar cell swelling, atrophy, and alterations in salivary flow rate, resulting in decreased salivary production [29]. Additionally, the presence of nicotine, as observed by Nigar et al. and Petrusic et al., may initially boost salivary flow rate but is followed by a subsequent decrease over time [2,22]. However, in the current study, no significant difference in salivary flow rate was noted. This discrepancy may be explained by the interaction between alcohol consumption and betel quid chewing in this demographic. While alcohol consumption tends to result in a drier oral cavity, betel quid chewing is associated with a higher salivary flow rate. When compared to individuals without risk factors, who typically exhibit normal salivary flow rates, there was no notable difference in salivary flow rate among this cohort. Furthermore, the duration of risk factor behavior (smoking, alcohol consumption, or betel quid chewing) did not affect salivary flow rate in this study. However, it is important to acknowledge that various factors such as stress, medication use, and salivary gland diseases may influence salivary production, potentially leading to xerostomia. These findings diverge slightly from earlier research, suggesting the presence of additional factors that may impact salivary flow rate [30].

According to Lin et al., Taiwanese natives commonly engage in the practice of betel quid usage, often accompanied by drinking and smoking [31]. Similarly, research by Rae et al. in India, Sri Lanka, and Pakistan reveals frequent engagement in bidi smoking, alcohol consumption, and chewing tobacco containing tobacco [32]. This suggests that populations across diverse countries face a multifactorial risk of oral cancer. Consistent with this notion, the population in Bajawa exhibits a variety of risk factor combinations, particularly involving the simultaneous consumption of alcohol and betel quid, compared to a single habit such as betel nut chewing alone. The synergistic effect of multiple hazardous behaviors, including betel quid chewing, smoking, and alcohol consumption, heightens the risk of Oral Potentially Malignant Disorders (OPMDs) and oral cancer [33]. In contrast to the findings of Amtha et al. in the Tanjung Pandang population, where individuals tended to have a single smoking habit, the average population displayed normal variant lesions and trauma lesions rather than OPMD lesions. This discrepancy may be attributed to the presence of only one risk factor for oral cancer in this group, which may be insufficient to cause OPMD lesions or oral cancer [34].

Comprising betel leaf, areca nut, and lime, betel quid represents the most prevalent form of chewing tobacco among the population of Flores, particularly in Bajawa. These findings align with qualitative research conducted concurrently by other scholars, indicating that chewing betel quid is widespread among the majority of the Bajawa population [5]. In western Indonesia, the combination typically includes betel leaf, gambier, and wet lime, whereas in eastern Indonesia, betel fruit, unripe areca nut, and dried lime are more commonly utilized [35]. According to the research findings of Sari et al., the levels of polyphenols and arecoline in areca nut seeds are directly correlated with their ripeness [36]. Young areca nuts are deemed more carcinogenic due to their higher concentrations of polyphenols and arecoline compared to older nuts [36]. Variations in the composition and usage practices of betel quid can lead to differing risks of oral cancer among individuals [35].

In this study, no significant difference was observed in the acidity of saliva between individuals with and without oral cancer risk factors (Figure 1). This finding contrasts

with previous research suggesting an increase in saliva pH among betel quid chewers. Additionally, Priyanka et al.'s study reported that although not statistically significant, the alcohol-drinking group exhibited lower salivary pH compared to the control group [37]. According to Singh et al., long-term smoking can lead to decreased salivary pH and flow rate [38]. The lack of a significant variation in salivary pH in our study may be attributed to similar saliva production rates between the betel nut and control groups. Moreover, the quantity of tobacco, lime, and other constituents consumed could potentially influence salivary pH. Lime contains a substantial concentration of alkali, which may impact the salivary buffer system's pH [28]. Furthermore, the impact of alcohol on the oral cavity depends on factors such as the beverage's composition, qualities, frequency, and quantity of consumption [37]. Additionally, salivary flow rate, which did not significantly differ between groups with and without risk factors in our study, may also affect saliva pH. Low salivary flow rates result in reduced bicarbonate concentration, leading to a decrease in salivary pH, and vice versa [38].

Interleukin-1 beta (IL-1β) has emerged as a pivotal player in the complex landscape of oral malignancies within the oral tumor microenvironment. The study made by Lee et al. regarding IL-1β as a mediator triggered by chronic inflammation, along with findings from previous studies, suggests that risk factors such as betel quid chewing, alcohol consumption, and smoking act as stimuli for inflammation, resulting in increased cytokine expression [23]. The Kaplan–Meier analysis depicted in Figure 2 shows the cumulative increase in IL-1β levels over time among individuals with different habits such as smoking, alcohol consumption, and betel quid chewing (BQC), both individually and in combination. The data indicate that alcohol consumption leads to a more rapid increase in IL-1β levels compared to smoking and BQC alone, suggesting a more immediate inflammatory response. When these habits are combined, the effect on IL-1β levels is even more pronounced, particularly in the group combining smoking, alcohol, and BQC, which shows the highest levels over time. This synergistic effect underscores the compounded risk of engaging in multiple harmful habits, contributing to elevated inflammatory markers. This condition is supported by the results of the study conducted in the Bajawa population, which revealed significantly higher levels of IL-1β in saliva among smokers compared to non-smokers. The heat generated by cigarette smoke and the interaction of nicotine with nitrites, leading to the formation of specific nitrosamines like 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone and 4-(methylnitrosamine)-1-(3-pyridil)-1-butanol, are known to trigger an inflammatory response. Prolonged exposure to cigarette smoke can induce a chronic inflammatory process, involving the recruitment of inflammatory cells, particularly macrophages. These macrophages play a crucial role in oral cancer development by releasing pro-inflammatory cytokines such as IL-1β and IL-8. Additionally, they contribute to the elevation of reactive oxygen species (ROS). Oxidative stress, resulting from an increase in ROS levels, leads to DNA damage and genomic instability, which are recognized mechanisms in cancer development. Therefore, the observed elevation in IL-1β levels in smokers could be indicative of the underlying inflammatory processes contributing to the pathogenesis of oral cancer [39].

The findings of this population-based study revealed a noteworthy disparity in IL-1β levels between individuals who consumed alcohol and those who did not, with higher IL-1β levels observed among alcohol consumers (Figure 1). Chronic alcohol consumption has been implicated in damaging oral mucosal tissue and triggering inflammation, which can subsequently induce IL-1β production. Key processes contributing to this phenomenon include oxidative stress and the breakdown of alcohol metabolites. Chronic alcohol intake leads to the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) during the conversion of ethanol into acetaldehyde. When the generation of ROS and RNS surpasses the body's antioxidant capacity, oxidative stress ensues. These free radicals are highly reactive and perceived as foreign agents by the immune system, prompting an enhanced secretion of cytokines and chemokines, including IL-1β [40]. Moreover, alcohol consumption interferes with the synthesis of collagen and other essential proteins

crucial for tissue repair and regeneration. Consequently, the impaired production of these proteins impedes the healing process of damaged oral mucosa, exacerbating persistent inflammation [41]. These mechanisms underscore the association between alcohol consumption and elevated IL-1β levels observed in this study, highlighting the detrimental effects of chronic alcohol use on oral health.

The research findings indicate a significant disparity in IL-1β levels between patients with and without risk factors (Figures 1 and 2). The observed elevation in IL-1β levels among individuals with risk factors aligns with the chronic inflammatory responses elicited by these factors. Previous studies have established a correlation between increased IL-1β levels and pathological changes conducive to the development of oral potentially malignant disorders (OPMDs) and cancer. Furthermore, it is plausible that genetic predispositions within this population contribute to their heightened susceptibility to cancer development [39]. This suggests a multifactorial etiology, wherein both environmental exposures and inherent genetic susceptibilities synergistically influence disease pathogenesis. This cytokine not only promotes tumor growth and invasion by stimulating angiogenesis and enhancing matrix metalloproteinases (MMPs) expression but also fosters an immunosuppressive milieu that aids in tumor evasion from immune surveillance. These findings underscore the intricate interplay between genetic factors, environmental exposures, and inflammatory processes in the initiation and progression of oral cancer.

According to studies conducted by Mio et al., the presence of acrolein and acetaldehyde in cigarette smoke can stimulate bronchial epithelial cells to produce higher levels of IL-8 [42]. Similarly, research by Huang et al. indicates that ethanol exposure can elevate plasma endotoxin levels and trigger the production of TNF-α and IL-1 [43]. These pro-inflammatory cytokines contribute to the augmentation of local and systemic IL-8 production in patients with alcoholic liver disease (ALD) [43]. In contrast to the marked increase observed in IL-1β levels, the rise in IL-8 levels appears to be less pronounced in this study. However, elucidating a direct correlation is complex. Sahibzada et al. demonstrated that various factors beyond exposure to risk factors can influence IL-8 levels, including lifestyle choices, geographical disparities, ethnic variations, genetic predispositions, and individual habits [44]. Moreover, findings from Vychaktami et al. suggest that certain dietary components commonly found in fruits and vegetables, such as curcumin, aloe vera, quercetin, and lycopene, possess anti-inflammatory properties and can inhibit the production of cytokines implicated in inflammation, including IL-1, IL-2, IL-6, IL-8, and IL-12 [45]. Consequently, it is plausible that the consumption of these dietary components may mitigate the elevation of IL-8 levels in individuals with risk factors [46]. This multifaceted interplay underscores the intricate mechanisms underlying cytokine regulation and the potential mitigating effects of dietary interventions on inflammation-associated pathways.

This study possesses several limitations that warrant acknowledgment. Firstly, the study did not account for the periodontal health status of participants, which may influence cytokine release in saliva. Secondly, the absence of information regarding the type of areca nut (unripe or overripe) utilized for betel nut chewing is pertinent, as it affects the alkaloid content in areca nut, potentially contributing to its carcinogenic properties. Additionally, the restricted saliva collection duration of 10 min may have led participants to inadvertently include mucoid substances in their samples, thereby impacting the assessment of salivary turbidity. Despite these limitations, the study's notable strength lies in being the first investigation of saliva profiles among individuals with oral cancer risk factors in East Indonesia, a region characterized by a high prevalence of such risk factors. As a recommendation for future research, it may be beneficial to include an evaluation of salivary antioxidants in relation to oral cancer susceptibility, thereby providing further insights into potential biomarkers for early detection and prevention strategies.

5. Conclusions

The present study uncovered differences in salivary IL-1β concentrations between individuals with and without habits linked to oral cancer risk. Nonetheless, no disparities

were detected in salivary viscosity, color, turbidity, flow rate, acidity, or IL-8 levels. These findings suggest that alterations in salivary profiles may hold promise as early indicators and novel diagnostic tools for identifying abnormalities within the oral cavity.

Author Contributions: Conceptualization, R.A., I.G. and F.K.H.; methodology, R.A. and A.S.W.; software, I.G.; validation, I.G., V.K.V.-C. and A.S.W.; formal analysis, I.G.; investigation, R.A. and T.H.; resources, R.A.; data curation, T.H.; writing—original draft preparation, T.H.; writing—review and editing, R.A. and I.G.; visualization, I.G.; supervision, R.A., A.S.W. and I.G.; project administration, T.H.; review, V.K.V.-C. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: This study was approved by the Ethics Commission of the Faculty of Dentistry, Universitas Trisakti (IRB number 022/S3/KEPK/FKG/7/2022).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patient(s) to publish this paper.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author, I.G. The data are not publicly available due to information that could compromise the privacy of research participants.

Conflicts of Interest: The authors declare no conflicts of interest.

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Journal: Biomedicines (https://www.mdpi.com/journal/biomedicines) (ISSN 2227-9059)

Manuscript ID: biomedicines-3118628

Type: Article

Title: Salivary profile analysis based on oral cancer risk habits

Authors: Rahmi Amtha , Indrayadi Gunardi * , Armelia Sari Widyarman , Tiffany Herwanto , Firstine Kelsi Hartanto , Vui King Vincent-Chong * (https://sciprofiles.com/profile/958587)

Section: Molecular and Translational Medicine (https://www.mdpi.com/journal/biomedicines/sections/medicine)

Special Issue: Oral Cancer: From Pathophysiology to Novel Therapeutic Approaches Volume II (https://www.mdpi.com/journal/biomedicines/special_issues/M7RIZN5ZC4)

Abstract: Background: In Indonesia, cultural practices such as betel quid chewing, smoking, and alcohol consumption are prevalent. These practices are known risk factors for oral cancer and may influence the salivary profile, which is essential for maintaining oral health. Purpose: to compare the salivary profiles of individuals with and without risk factors for oral cancer. Methods: The study included 49 individuals identified as having risk factors for oral cancer. Unstimulated saliva samples were collected. Various parameters were measured, including salivary pH, flow rate (FR), thickness, color, turbidity, and levels of IL-1β and IL-8. Data were analyzed using Chi-square and t-tests. Results: A significant difference was found in salivary IL-1β levels between the two groups (p=0.009), with higher levels observed in individuals with oral cancer risk factors. Notably, the salivary IL-1β concentrations showed significant differences between the smoking group (p=0.021; OR=2.94) and the alcohol-drinking group (p=0.007; OR=4.96) compared to the control group. However, no significant differences were found between the groups in terms of salivary viscosity, color, turbidity, flow rate, acidity, or IL-8 levels (p>0.05). Conclusion: Individuals with risk factors for oral cancer exhibit distinct salivary IL-1β profiles compared to those without such risk factors, particularly those who practice alcohol drinking.

Author's Reply to the Review Report (Reviewer 1)

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Does the introduction provide sufficient background and include all relevant references?	(x)	( )	( )	( )
Is the research design appropriate?	(x)	( )	( )	( )
Are the methods adequately described?	(x)	( )	( )	( )
Are the results clearly presented?	(x)	( )	( )	( )
Are the conclusions supported by the results?	(x)	( )	( )	( )

Comments and

Suggestions for Authors

Overall, I found the article well-structured and with a clear methodology. The results are discussed in detail, and the findings match the presentations in the tables and figures.

However, several minor English and grammatical errors should be corrected for better clarity and readability.

For instance,

Abstract:

"Purpose: to compare" should be "Purpose: To compare".

"turbidity, and levels of IL-1β and IL-8." should be "turbidity, and the levels of IL-1β and IL-8."

"various parameters were measured" should be "Various parameters were measured".

"Data were analyzed using Chi-square and t- tests." should be "Data were analyzed using Chi-square and *t*-tests."

"No significant differences were found between the groups in terms of" can be improved to "No significant differences were observed between the groups in terms of."

Introduction:

"WHO estimates that the majority of oral and oropharyngeal cancer cases globally, around 58%, occur in South Asia and Southeast Asia, including Indonesia." This can be simplified for clarity: "WHO estimates that around 58% of global oral and oropharyngeal cancer cases occur in South and Southeast Asia, including Indonesia."

The citation format should be consistent throughout the document. For example, "[2];[3]" should be "[2,3]".

"and non-routine smokers as high as 7.3%, as well as the second highest province with a proportion" should be "and non-routine smokers at 7.3%. It is also the second highest province with a proportion".

Results:

"Table 1 showed significant differences" should be "Table 1 shows significant differences".

"In this study, a significant risk factor for oral cancer is the simultaneous consumption" should be "In this study, the simultaneous consumption."

"Notably, the habit of alcohol consumption appears" should be "Notably, alcohol consumption appears."

Comments on the Quality of English Language	Needs thorough language edits.
Submission Date	06 July 2024
Date of this review	19 Jul 2024 18:18:50

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Manuscript ID: biomedicines-3118628

Type: Article

Title: Salivary profile analysis based on oral cancer risk habits

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Section: Molecular and Translational Medicine (https://www.mdpi.com/journal/biomedicines/sections/medicine)

Special Issue: Oral Cancer: From Pathophysiology to Novel Therapeutic Approaches Volume II (https://www.mdpi.com/journal/biomedicines/special_issues/M7RIZN5ZC4)

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Author's Reply to the Review Report (Reviewer 2)

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	Yes	Can be improved	Must be improved	Not applicable
Does the introduction provide sufficient background and include all relevant references?	( )	(x)	( )	( )
Is the research design appropriate?	( )	(x)	( )	( )
Are the methods adequately described?	( )	(x)	( )	( )
Are the results clearly presented?	( )	(x)	( )	( )
Are the conclusions supported by the results?	( )	(x)	( )	( )

Comments and
The aim of the present investigation was to compare the salivary profiles of individuals with and without risk factors for oral cancer.

Suggestions for Authors

GENERAL COMMENTS

The article is in-line with the journal topic, but flaws should be improved. The investigation is interesting, and the present paper is recommended for publication to the present journal after major revision.

Title: The title should indicate the type of study that has been conducted: (f.e.: Salivary profile analysis based on oral cancer risk habits: an observational cross-sectional study)

Introduction

1. The authors should support the biological basis of the biomarker chosen.

2. Il-1beta and IL-8 seems to be pro-inflammatory aspecific markers involved in carcinogenesis but also a wide quantity of oral disease. The interleukins detected in oral saliva could easily misinterpreted (f.e. periodontitis, gingivitis….). The physiological level of salivary Il-1beta and IL-8 should be declared.

3. The authors considered color, turbidity, viscosity, and pH of saliva as potential predictors for oral carcinogenesis risk. If applicable, the authors should support the biological bases with references.

Materials and methods

1. The inclusion and exclusion criteria section is missed.

2. Did you considered also subjects with oral cancer?

3. “Saliva collection procedures were conducted in the morning, with subjects instructed to refrain from eating, drinking, smoking, or chewing betel quid for a period of 60 minutes prior to collection”. In my opinion, also oral rinses with antiseptics and teeth brushing could modify the salivary properties.

4. The present study design did not take in account any quantitative predictor for smoking, betel fruit, betel leaf, areca nut, lime consumption. What was the inferior limit of consumption/die for each predictor?

5. A repository for raw metadata access should be added to the present study as supplemental material.

Results

The result section is weak. The present investigation did not consider other independent risk factor (f.e. familiarity). In my opinion, the validation process should take in account a stronger study design for this purpose (f.e. RCT).

The authors did not take in account the combination of risk factor in Il-1beta and IL-8. It could be interesting to verify the power effect and the synergy of the predictors considered.

Discussion

The authors should discuss the oral cancer epidemiology, physiopathology, clinical course, TNM and characteristics. The risk factors should be discussed in a more accurate way. In addition, several potential salivary biomarkers (including mRNA detection) have been purposed for this scope as in-chair test for primary prevention. The future perspective of this application is certainly interesting but the critical limit of the present study design is the model validation. The Il-1beta and IL-8 correlation with oral cancer is weak and too aspecific for a cross-sectional study design.. In contrary, the study model should include a test group (f.e. patients affected by oral cancer) and a control group.

Submission Date	06 July 2024
Date of this review	16 Jul 2024 10:22:59

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Authors: Rahmi Amtha , Indrayadi Gunardi * , Armelia Sari Widyarman , Tiffany Herwanto , Firstine Kelsi Hartanto , Vui King Vincent-Chong * (https://sciprofiles.com/profile/958587)

Section: Molecular and Translational Medicine (https://www.mdpi.com/journal/biomedicines/sections/medicine)

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Abstract: Background: In Indonesia, cultural practices such as betel quid chewing, smoking, and alcohol consumption are prevalent. These practices are known risk factors for oral cancer and may influence the salivary profile, which is essential for maintaining oral health. Purpose: to compare the salivary profiles of individuals with and without risk factors for oral cancer. Methods: The study included 49 individuals identified as having risk factors for oral cancer. Unstimulated saliva samples were collected. Various parameters were measured, including salivary pH, flow rate (FR), thickness, color, turbidity, and levels of IL-1β and IL-8. Data were analyzed using Chi-square and t-tests. Results: A significant difference was found in salivary IL-1β levels between the two groups (p=0.009), with higher levels observed in individuals with oral cancer risk factors. Notably, the salivary IL-1β concentrations showed significant differences between the smoking group (p=0.021; OR=2.94) and the alcohol-drinking group (p=0.007; OR=4.96) compared to the control group. However, no significant differences were found between the groups in terms of salivary viscosity, color, turbidity, flow rate, acidity, or IL-8 levels (p>0.05). Conclusion: Individuals with risk factors for oral cancer exhibit distinct salivary IL-1β profiles compared to those without such risk factors, particularly those who practice alcohol drinking.

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Does the introduction provide sufficient background and include all relevant references?	( )	(x)	( )	( )
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Are the methods adequately described?	(x)	( )	( )	( )
Are the results clearly presented?	(x)	( )	( )	( )
Are the conclusions supported by the results?	(x)	( )	( )	( )

Comments and
This is an interesting study on salivary profile analysis of oral cancer risk habits in Indonesian patients.

Suggestions for Authors	The article is well written, clear to read, and the results are well presented. The Tables are easy to read, only Figure 2 could be slightly enlarged. Here are my comments: The introduction could be a little more extensive on saliva (role, properties, etc.). In the materials and methods section, it would be interesting not only to provide the duration of the habits of the patients, but also the daily amount. It would have been interesting to have a control group of patients with precancerous lesions or squamous cell carcinoma. In the discussion, the role of IL1β in the process of malignant transformation should be further discussed. Finally may be 49 patients is a limited number of tested subjects
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Salivary Profile Analysis Based on Oral Cancer Risk Habits: An Observational Cross-Sectional Study

by Rahmi Amtha

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Salivary Profile Analysis Based on Oral Cancer Risk Habits: An Observational Cross-Sectional Study

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Abstract: Background: In Indonesia, cultural practices such as betel quid chewing, smoking, and alcohol consumption are prevalent. These practices are known risk factors for oral cancer and may influence the salivary profile, which is essential for maintaining oral health. Purpose: To compare the salivary profiles of individuals with and without risk factors for oral cancer. Methods: The study included 49 individuals identified as having risk factors for oral cancer. Unstimulated saliva samples were collected. Various parameters were measured, including salivary pH, flow rate (FR), thickness, color, turbidity, and the levels of IL-1β and IL-8. Data were analyzed using Chi-square and *t*-tests. Results: A significant difference was found in salivary IL-1β levels between the two groups ($p = 0.009$), with higher levels observed in individuals with oral cancer risk factors. Notably, the salivary IL-1β concentrations showed significant differences between the smoking group ($p = 0.021$; OR = 2.94) and the alcohol-drinking group ($p = 0.007$; OR = 4.96) compared to the control group. However, no significant differences were observed between the groups in terms of salivary viscosity, color, turbidity, flow rate, acidity, or IL-8 levels ($p > 0.05$). Conclusion: Individuals with risk factors for oral cancer exhibit distinct salivary IL-1β profiles compared to those without such risk factors, particularly those who practice alcohol drinking.

Keywords: risk factor; saliva; oral cancer

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1. Introduction

The World Health Organization (WHO) estimates that around 58% of global oral and oropharyngeal cancer cases occur in South and Southeast Asia, including Indonesia [1]. Various risk factors contribute to the development of oral cancer, including tobacco smoking, alcohol consumption, chronic inflammation, human papillomavirus (HPV), genetic predisposition, and dietary habits [2,3].

Each province in Indonesia has its distinct traditions and cultures. The practice of chewing betel quid, a tradition passed down through generations, is prevalent. In 2004, the International Agency for Research on Cancer (IARC) classified betel quid chewing, with or without tobacco, as carcinogenic to humans [4]. The consumption of alcoholic beverages, particularly a traditional alcohol known as "moke" or "sopi" derived from palm tree sap with a high ethanol content, is another prevalent habit among the Flores population [5]. According to the 2018 Indonesian National Health Survey, smoking prevalence in Indonesia is significant, with East Nusa Tenggara having notably high rates of 19% and non-routine smokers at 7.3%. It is also the second-highest province with a

proportion of the consumption of alcoholic beverages in the past month of 15.6%. Tobacco exposure, a component of smoking, is a significant risk factor for oral cancer [6].

Saliva plays a crucial role in maintaining oral health through various functions and properties. It acts as a lubricant, aiding in chewing, swallowing, and speaking, while forming a protective barrier against mechanical damage and pathogens [7]. Saliva, as a bodily fluid, reflects various physiological and pathological conditions. It is easily accessible, cost-effective, and non-invasive, making it an ideal medium for diagnostic purposes [8,9]. Saliva has a buffering capacity that neutralizes acids produced by bacteria, preventing tooth enamel demineralization and promoting remineralization. Its antimicrobial agents, such as lysozyme and lactoferrin, control the growth of oral microbiota and prevent infections [10]. It also acts as a solvent for taste substances, facilitating interaction with taste receptors and maintaining taste buds [11]. Saliva is primarily composed of water (99%) along with electrolytes, mucus, antibacterial compounds, and enzymes. Its viscosity, influenced by mucin glycoproteins, is essential for its lubricating function [12]. Salivary flow rate varies with factors like hydration and diet, with a normal unstimulated flow at 0.3–0.4 mL/min and stimulated flow at 1–2 mL/min [13]. The pH of saliva ranges from 6.2 to 7.6, maintained by bicarbonate, phosphate, and protein systems, contributing to its buffering capacity [14]. In the presence of a tumor, the pH of saliva becomes acidic. This change is due to the anaerobic metabolism of glucose under the hypoxic conditions created by the tumor. The acidic environment provides a supportive setting for a tumor cell to survive and proliferate [15]. Saliva contains proteins, including cytokines, which have been identified as potential biomarkers for various diseases, including oral cancer. IL-8 and IL-1β, cytokines implicated in processes such as replication, angiogenesis, and tumor development, are particularly relevant in oral cancer diagnosis [15–17]. Several studies have indicated that salivary cytokines may serve as diagnostic biomarkers for various diseases, including oral cancer. Pro-inflammatory cytokines such as IL-1β, IL-6, IL-8, INF-γ, and TNF-α are known to enhance cell growth, disrupt tumor suppression mechanisms, and impair host immunity, leading to cancer progression. Hence, over 100 potential biomarkers for detecting oral cancer have been observed, with IL-8 and IL-1β playing crucial roles in cell replication, angiogenesis, cell adhesion, and tumor development. Several studies have detected IL-1β and IL-8 in the serum and saliva (IL-1β 0.5–12 pg/mL; IL-8 < 62 pg/mL) of patients with oral squamous cell carcinoma (OSCC), highlighting their significance as biomarkers for oral cancer [18,19]. Studies have shown their presence in the serum and saliva of patients with OSCC, underscoring their significance as biomarkers [20].

Given the prevalence of oral cancer risk habits in communities like betel nut chewing, alcohol consumption, and smoking, it is hypothesized that these practices may influence salivary profiles, impacting oral health. However, research on the salivary profile within these communities, especially in Flores, East Nusa Tenggara, where such cultural practices are prominent, remains scarce. Hence, this study aimed to assess the salivary profile of individuals with and without oral cancer risk habits in this context.

2. Materials and Methods

This observational cross-sectional study involved 77 subjects, comprising 49 individuals with identified risk habits and 28 without such habits, conducted on Flores Island, East Nusa Tenggara province. The determination of the sample size was based on parameters derived from previous studies, specifically an effect size of 1.72 as reported by Amtha et al. (2015), with a study power of 95% and a significance level (α) set at 0.05, calculated using G*Power 3.1.9.7 software [5].

Inclusion criteria encompassed individuals with a history of betel nut chewing, alcohol consumption, and/or smoking for a minimum duration of 1 year. Conversely, exclusion criteria were applied to subjects currently taking antibiotics, antihistamines, or long-term steroids, undergoing cancer treatment, or presenting with cancerous lesions in other organs. All participants provided informed consent before data collection commenced.

Ethical approval for the study was obtained from the Ethics Commission of the Faculty of Dentistry, University of Trisakti, under reference number 022/S3/KEPK/FKG/7/2022.

2.1. Collection of Unstimulated Salivary Samples

Saliva collection procedures were conducted in the morning, with subjects instructed to refrain from eating, drinking, smoking, or chewing betel quid for a period of 60 min prior to collection. The saliva collection method employed was the spitting technique, where participants were instructed to expectorate saliva into a falcon tube for a duration of 10 min.

2.2. Assessment of the Color, Turbidity, Viscosity, and pH of Saliva

The assessment of color and turbidity was conducted through visual inspection by two calibrated oral medicine specialists. Salivary acidity levels were measured using a digital pH meter (Mediatech pH Meter Digital Automatic Calibration P-2Z), which was calibrated beforehand using 6.86 and 4.00 buffers.

2.3. Examination of IL-1β and IL-8 Levels Using an Enzyme-Linked Immunosorbent Assay (ELISA)

Salivary protein separation was conducted using the Genezol Kit (Geneaid, Cat# GZR200). The process involved sample homogenization, followed by the separation of RNA, DNA, and protein in saliva samples. Protein extraction, deposition, washing, and resuspension were then performed to obtain the protein fraction.

Subsequently, the levels of IL-1β and IL-8 (expressed in pg/mL) in saliva were determined utilizing the ELISA method. For this purpose, primers and technical materials specific to IL-1β and IL-8 were utilized (Bioassay Technology Laboratories, Cat# E0143HU, E0089HU). Sample testing was conducted in duplicate to ensure accuracy and reliability.

The optical density values in each well were measured using a microplate reader set to a wavelength of 450 nm. This facilitated the quantification of IL-1β and IL-8 levels in the saliva samples, providing valuable insights into their concentrations.

2.4. Data Analysis

Bivariate analysis was conducted using the Chi-square test for non-parametric data and the t-test for normally distributed data. A significance level of $p < 0.05$ was deemed statistically significant in determining differences between groups. Odds ratios were calculated to assess the significance of cytokine levels between the groups, providing further insight into the associations observed. Additionally, Kaplan–Meier analysis was used to determine the interleukin level.

3. Results

3.1. Subject Characteristics

Table 1 shows significant differences in risk factors based on gender ($p = 0.007$). Both males (93.33%) and females (56.4%) exhibited a higher prevalence of risk factors compared to those without such factors. Males primarily presented with smoking and alcohol consumption habits (18.37%), while females predominantly engaged in drinking alcohol and betel quid chewing (38.78%). Additionally, there was a notable disparity in risk factors across age groups ($p = 0.035$), with individuals over 35 demonstrating a higher propensity for risk factors compared to those under 35. Among the 77 study participants, no significant differences were observed in salivary viscosity ($p = 0.459$), color ($p = 0.476$), turbidity ($p = 1.000$), and salivary flow rate ($p = 0.235$) between subjects with and without risk factors.

In this study, the simultaneous consumption of alcohol and betel quid accounts for 38.77% of the population. Additionally, betel quid chewing alone is prevalent (24.48%) in the population. Filter cigarettes are the predominant type of tobacco product used in the

region. The preferred alcoholic beverage among community members is "moke putih or tua bhara". The common composition of betel quid typically includes a mixture of inflorescence betel leaves, unripe areca nut, and lime.

Table 1. Population characteristics.

Variable	Risk Factor		Non-Risk Factors		Total	*p*-Values
	n	%	n	%	n	
Gender						
Male	14	93.33	1	6.67	15	0.008 **
Female	35	56.45	27	43.55	62	
Age (years)						
<35.3	12	46.15	14	53.85	26	0.035 *
>35.3–42.7	16	64	9	36	25	
>42.7	21	80.77	5	19.23	26	
Salivary viscosity						
Dilute	30	60	20	40	50	0.459
Thick	19	70.37	8	29.63	27	
Color						
Colorless	29	60.42	19	39.58	48	0.476
Colored	20	68.97	9	31.03	29	
Turbidity						
Clear	8	61.54	5	38.46	13	1.000
Cloudy	41	64.06	23	35.94	64	
Salivary flow rate (mL/10 min)						
<3.2	20	55.55	16	44.44	36	0.235
>3.2	29	70.73	12	29.27	41	
Risk factor habit						
Smoking (S)	1	2.04	-	-	1	
Alcohol drinking (A)	5	10.2	-	-	5	
BQ Chewing (BQ)	12	24.48	-	-	12	
S + A	10	20.40	-	-	10	
S + BQ	1	2.04	-	-	1	
A + BQ	19	38.77	-	-	19	
S + A + BQ	1	2.04	-	-	1	
BQ Chewing composition						
Betel leaf, areca nut, lime	16	100	-	-	16	
Betel leaf, areca nut, lime, tobacco	1	100	-	-	1	
Betel fruit, areca nut, lime	2	100	-	-	2	
Betel fruit, betel leaf, areca nut, lime	13	100	-	-	13	
Betel fruit, betel leaf, areca nut, lime, gambier, tobacco	1	100	-	-	1	

S, smoking; A, alcohol drinking; BQ, betel quid; * $p < 0.01$; ** $p < 0.05$.

3.2. pH, Salivary Flow Rates, and Interleukin Level between Risk Factor Groups

Figure 1 showed the disparities among community cohorts, categorized by the presence or absence of risk factors for oral cancer. Notably, a substantial difference was found in the salivary IL-1β profile between these cohorts, where individuals with identified risk factors exhibit markedly elevated IL-1β levels. Subsequent examination discloses noteworthy variations in IL-1β concentrations between smokers and non-smokers, as smokers

demonstrate notably augmented IL-1β levels compared to their non-smoking counterparts. Similarly, a conspicuous distinction emerges in IL-1β concentrations between alcohol consumers and non-consumers, as the former exhibit higher IL-1β levels. Conversely, IL-8 levels do not manifest significant disparities across the cohorts.

Figure 2 describes that IL-1β levels may increase with prolonged use of tobacco, alcohol, and betel quid. Kaplan–Meier analysis showed that the mean estimated time for elevated IL-1β levels was 27.90 months (22.47–33.34). Notably, alcohol consumption appears to accelerate the increase in IL-1β levels more rapidly compared to other oral cancer risk factors.

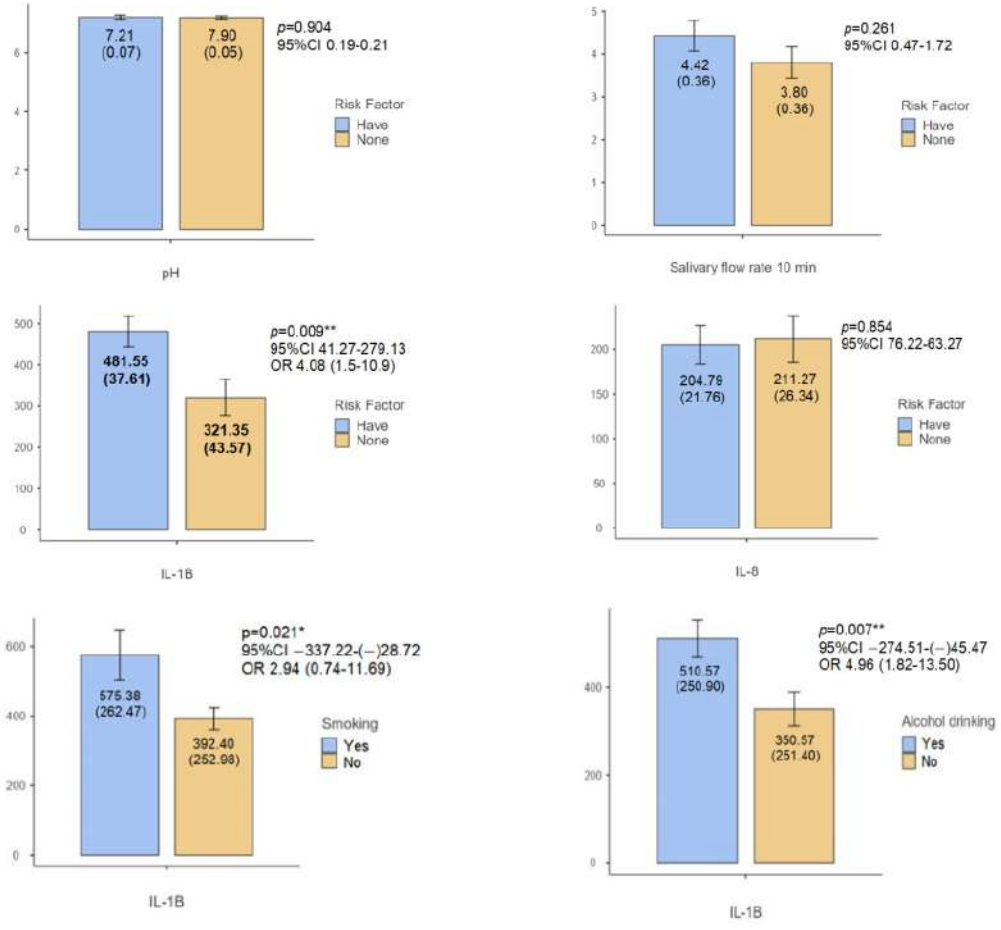

Figure 1. Bar chart showing the mean and standard deviation of pH, salivary flow rate, IL-1β, IL-8 among the studied groups. ** $p < 0.01$ * $p < 0.05$.

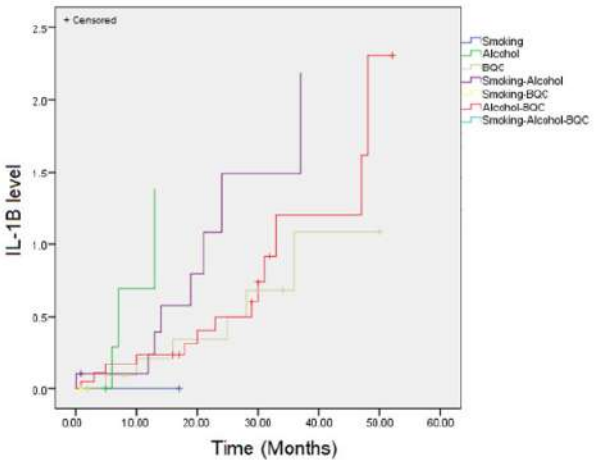

Figure 2. Kaplan–Meier analysis of time to IL-1β level among the groups.

3.3. Correlation between Duration of Risk Factor Habit and Salivary Viscosity

Table 2 shows the absence of a correlation between salivary viscosity and the duration of exposure to risk factors, including smoking, alcohol consumption, or betel nut chewing.

Table 2. Salivary viscosity and duration of risk factor habit.

Variable	Duration (year)					
	Smoking		Alcohol Drinking		Betel Quid Chewing	
	Mean (SD)	*p*	Mean (SD)	*p*	Mean (SD)	*p*
Salivary viscosity		0.22		0.151		0.526
Dilute	22.94 (11.91)		16.60 (12.92)		17.42 (11.25)	
Thick	29.73 (18.28)		24.84 (19.30)		23.80 (22.26)	
Duration habit	20.08 (16.12)		19.85 (15.98)		25.79 (15.02)	

3.4. Comparison of Duration of Risk Factor Habit and Salivary Flow Rate

Table 2 shows that betel nut chewing has been the longest-standing risk factor among the study population, with an average duration of 25.79 years. However, the duration of habits such as smoking, alcohol consumption, and betel nut chewing did not significantly impact the salivary flow rate ($p > 0.05$) (Figure 3). In Figure 4, subjects with a habit of betel nut chewing demonstrate the highest salivary flow rate, followed by those who combine alcohol consumption with betel nut chewing.

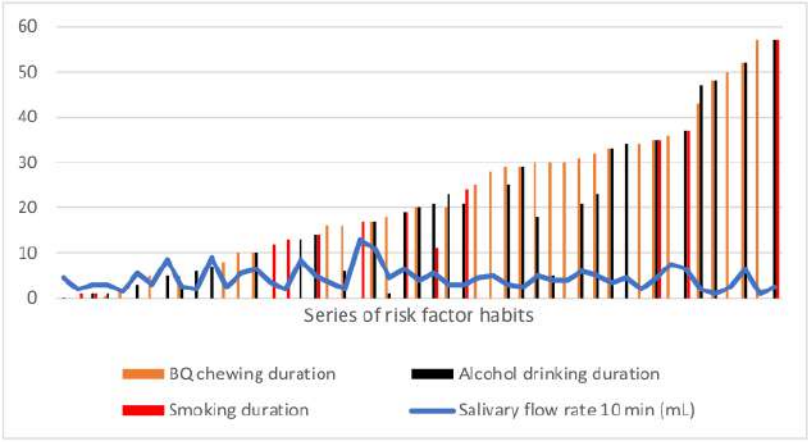

Figure 3. Series of risk factor habits based on the duration and salivary flow rate 10 min. (BQC, betel quid chewing).

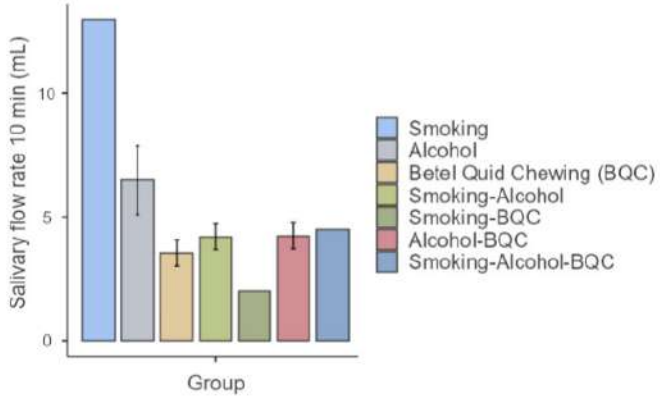

Figure 4. The salivary flow rates over a 10 min period vary across different risk factor habit groups as follows: smoking: 13.0 mL; alcohol: 6.50 (3.10) mL; betel quid chewing (BQC): 3.54 (1.86) mL; smoking–alcohol: 4.20 (1.64) mL; smoking–BQC: 2 mL; alcohol–BQC: 4.24 (2.28) mL; smoking–alcohol–BQC: 4.50 mL.

4. Discussion

Based on gender, the proportion of individuals with risk factors exceeded those without risk factors, 63.64% and 36.36%, respectively (Table 1). The most prevalent risk factor among males is the combined use of alcohol and smoking, consistent with data from the Indonesian Health National Survey indicating a higher prevalence of male smokers (47.3%) compared to females (1.2%) among individuals aged ≥10 years. Conversely, females predominantly engage in the combined consumption of alcohol and betel quid. According to a study by Amtha et al., locals perceive chewing betel leaves as invigorating and fatigue-reducing [5]. Both genders in the Bajawa region exhibit a significant inclination towards alcohol consumption, often attributed to the cold climate, which prompts locals to use alcohol for warmth [5]. Additionally, locals are known for producing homemade alcohol, referred to as "moke," commonly consumed during traditional ceremonies.

This study showed that individuals aged over 35 exhibit a higher prevalence of risk factors compared to those under 35 (Table 1). In a result consistent with the research conducted by Amtha R et al., a significant proportion of betel quid chewers and alcohol

drinkers are elderly individuals [5]. Moreover, data from the Global Adult Tobacco Survey (GATS) 2021 indicates that smoking in the Indonesian population is most prevalent among individuals aged 25 to 44.

In this study, no significant difference was observed in the viscosity of saliva between participants with and without oral cancer risk factors (Figure 1 and Table 2). This lack of disparity can be attributed to the distinct effects of smoking, alcohol consumption, and betel quid chewing on salivary viscosity. Chronic alcohol consumption, as noted by Bronislaw L, leads to increased TNF expression and acinar cell apoptosis, potentially diminishing salivary function and production, consequently elevating saliva viscosity [21]. Studies by Nigar et al. and Petrušić et al. have indicated that smokers typically exhibit thicker saliva compared to non-smokers, potentially as a compensatory mechanism by salivary glands against the continuous deposition of toxins from cigarette compounds [22,23]. Conversely, research by Reddy et al. suggests that prolonged betel quid chewing may lead to a more watery salivation, possibly due to lower levels of potassium and amylase in the saliva of betel nut chewers [24]. In individuals with risk factors, there is no correlation observed between the duration of smoking ($p = 0.22$), alcohol consumption ($p = 0.151$), betel quid chewing ($p = 0.526$), and salivary viscosity (Figure 3). Notably, betel quid chewing poses the second-highest risk factor, resulting in a tendency for saliva viscosity to resemble that of the majority of patients without risk factors.

According to Anand et al., the habit of chewing betel quid often results in the production of blood-red saliva, with the stain becoming ingrained in the teeth, gums, and oral mucosa over time [25]. In the present study, no significant difference in saliva color was observed between patients with risk factors for oral cancer and those without ($p = 0.476$) (Table 1). This lack of distinction may be attributed to the study participants, the majority of whom exhibited high-risk behaviors such as alcohol consumption and betel quid chewing. The presence of high levels of ethanol in saliva due to alcohol consumption can have a solubilizing effect, leading to oral mucosa dryness. Consequently, the color of betel quid constituents may be dissolved, resulting in a lack of discernible differences between patients with and without risk factors.

Areca nut, a key component of betel quid, contains tannin, as identified by Horne et al. [26]. High salivary protein levels, induced by areca nut consumption, can lead to turbidity in saliva. Furthermore, the interaction between tannins and proteins forms a precipitate, resulting in astringency and haze development [26,27]. The study reported both patients with and without risk factors demonstrated a relatively high salivary flow rate, potentially increasing saliva's protein content and causing cloudiness. Subjects with risk factors also exhibited cloudy saliva, possibly due to lime present in the betel nut. Conversely, in the group without risk factors, turbidity may have been influenced by the limited saliva collection time of 10 min, during which participants typically expectorate saliva, leading to subconscious mucoid engagement and increased salivary turbidity.

In this study, no significant difference was found in the salivary flow rates between individuals with and without oral cancer risk factors ($p = 0.235$) (Table 1 and Figure 4). Notably, subjects with a singular habit of betel quid chewing exhibited the highest salivary flow rate, consistent with findings by Rooban et al., who reported that betel quid chewers had greater salivary flow rates compared to non-chewers [28]. This phenomenon is attributed to the enlargement of salivary glands resulting from persistent betel quid chewing, leading to an elevated salivary flow rate [28]. Contrary to the above, chronic alcoholics are prone to experiencing dry mouth, as suggested by Innenaga et al. The accumulation of ethanol and acetaldehyde can induce apoptosis and cell death in acinar cells, while alcohol intake may also lead to fat accumulation in salivary glands, acinar cell swelling, atrophy, and alterations in salivary flow rate, resulting in decreased salivary production [29]. Additionally, the presence of nicotine, as observed by Nigar et al. and Petrusic et al., may initially boost salivary flow rate but is followed by a subsequent decrease over time [2,22]. However, in the current study, no significant difference in salivary flow rate was noted. This discrepancy may be explained by the interaction between alcohol

consumption and betel quid chewing in this demographic. While alcohol consumption tends to result in a drier oral cavity, betel quid chewing is associated with a higher salivary flow rate. When compared to individuals without risk factors, who typically exhibit normal salivary flow rates, there was no notable difference in salivary flow rate among this cohort. Furthermore, the duration of risk factor behavior (smoking, alcohol consumption, or betel quid chewing) did not affect salivary flow rate in this study. However, it is important to acknowledge that various factors such as stress, medication use, and salivary gland diseases may influence salivary production, potentially leading to xerostomia. These findings diverge slightly from earlier research, suggesting the presence of additional factors that may impact salivary flow rate [30].

According to Lin et al., Taiwanese natives commonly engage in the practice of betel quid usage, often accompanied by drinking and smoking [31]. Similarly, research by Rae et al. in India, Sri Lanka, and Pakistan reveals frequent engagement in bidi smoking, alcohol consumption, and chewing tobacco containing tobacco [32]. This suggests that populations across diverse countries face a multifactorial risk of oral cancer. Consistent with this notion, the population in Bajawa exhibits a variety of risk factor combinations, particularly involving the simultaneous consumption of alcohol and betel quid, compared to a single habit such as betel nut chewing alone. The synergistic effect of multiple hazardous behaviors, including betel quid chewing, smoking, and alcohol consumption, heightens the risk of Oral Potentially Malignant Disorders (OPMDs) and oral cancer [33]. In contrast to the findings of Amtha et al. in the Tanjung Pandang population, where individuals tended to have a single smoking habit, the average population displayed normal variant lesions and trauma lesions rather than OPMD lesions. This discrepancy may be attributed to the presence of only one risk factor for oral cancer in this group, which may be insufficient to cause OPMD lesions or oral cancer [34].

Comprising betel leaf, areca nut, and lime, betel quid represents the most prevalent form of chewing tobacco among the population of Flores, particularly in Bajawa. These findings align with qualitative research conducted concurrently by other scholars, indicating that chewing betel quid is widespread among the majority of the Bajawa population [5]. In western Indonesia, the combination typically includes betel leaf, gambier, and wet lime, whereas in eastern Indonesia, betel fruit, unripe areca nut, and dried lime are more commonly utilized [35]. According to the research findings of Sari et al., the levels of polyphenols and arecoline in areca nut seeds are directly correlated with their ripeness [36]. Young areca nuts are deemed more carcinogenic due to their higher concentrations of polyphenols and arecoline compared to older nuts [36]. Variations in the composition and usage practices of betel quid can lead to differing risks of oral cancer among individuals [35].

In this study, no significant difference was observed in the acidity of saliva between individuals with and without oral cancer risk factors (Figure 1). This finding contrasts with previous research suggesting an increase in saliva pH among betel quid chewers. Additionally, Priyanka et al.'s study reported that although not statistically significant, the alcohol-drinking group exhibited lower salivary pH compared to the control group [37]. According to Singh et al., long-term smoking can lead to decreased salivary pH and flow rate [38]. The lack of a significant variation in salivary pH in our study may be attributed to similar saliva production rates between the betel nut and control groups. Moreover, the quantity of tobacco, lime, and other constituents consumed could potentially influence salivary pH. Lime contains a substantial concentration of alkali, which may impact the salivary buffer system's pH [28]. Furthermore, the impact of alcohol on the oral cavity depends on factors such as the beverage's composition, qualities, frequency, and quantity of consumption [37]. Additionally, salivary flow rate, which did not significantly differ between groups with and without risk factors in our study, may also affect saliva pH. Low salivary flow rates result in reduced bicarbonate concentration, leading to a decrease in salivary pH, and vice versa [38].

Interleukin-1 beta (IL-1β) has emerged as a pivotal player in the complex landscape of oral malignancies within the oral tumor microenvironment. The study made by Lee et al. regarding IL-1β as a mediator triggered by chronic inflammation, along with findings from previous studies, suggests that risk factors such as betel quid chewing, alcohol consumption, and smoking act as stimuli for inflammation, resulting in increased cytokine expression [23]. The Kaplan–Meier analysis depicted in Figure 2 shows the cumulative increase in IL-1β levels over time among individuals with different habits such as smoking, alcohol consumption, and betel quid chewing (BQC), both individually and in combination. The data indicate that alcohol consumption leads to a more rapid increase in IL-1β levels compared to smoking and BQC alone, suggesting a more immediate inflammatory response. When these habits are combined, the effect on IL-1β levels is even more pronounced, particularly in the group combining smoking, alcohol, and BQC, which shows the highest levels over time. This synergistic effect underscores the compounded risk of engaging in multiple harmful habits, contributing to elevated inflammatory markers. This condition is supported by the results of the study conducted in the Bajawa population, which revealed significantly higher levels of IL-1β in saliva among smokers compared to non-smokers. The heat generated by cigarette smoke and the interaction of nicotine with nitrites, leading to the formation of specific nitrosamines like 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone and 4-(methylnitrosamine)-1-(3-pyridil)-1-butanol, are known to trigger an inflammatory response. Prolonged exposure to cigarette smoke can induce a chronic inflammatory process, involving the recruitment of inflammatory cells, particularly macrophages. These macrophages play a crucial role in oral cancer development by releasing pro-inflammatory cytokines such as IL-1β and IL-8. Additionally, they contribute to the elevation of reactive oxygen species (ROS). Oxidative stress, resulting from an increase in ROS levels, leads to DNA damage and genomic instability, which are recognized mechanisms in cancer development. Therefore, the observed elevation in IL-1β levels in smokers could be indicative of the underlying inflammatory processes contributing to the pathogenesis of oral cancer [39].

The findings of this population-based study revealed a noteworthy disparity in IL-1β levels between individuals who consumed alcohol and those who did not, with higher IL-1β levels observed among alcohol consumers (Figure 1). Chronic alcohol consumption has been implicated in damaging oral mucosal tissue and triggering inflammation, which can subsequently induce IL-1β production. Key processes contributing to this phenomenon include oxidative stress and the breakdown of alcohol metabolites. Chronic alcohol intake leads to the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) during the conversion of ethanol into acetaldehyde. When the generation of ROS and RNS surpasses the body's antioxidant capacity, oxidative stress ensues. These free radicals are highly reactive and perceived as foreign agents by the immune system, prompting an enhanced secretion of cytokines and chemokines, including IL-1β [40]. Moreover, alcohol consumption interferes with the synthesis of collagen and other essential proteins crucial for tissue repair and regeneration. Consequently, the impaired production of these proteins impedes the healing process of damaged oral mucosa, exacerbating persistent inflammation [41]. These mechanisms underscore the association between alcohol consumption and elevated IL-1β levels observed in this study, highlighting the detrimental effects of chronic alcohol use on oral health.

The research findings indicate a significant disparity in IL-1β levels between patients with and without risk factors (Figures 1 and 2). The observed elevation in IL-1β levels among individuals with risk factors aligns with the chronic inflammatory responses elicited by these factors. Previous studies have established a correlation between increased IL-1β levels and pathological changes conducive to the development of oral potentially malignant disorders (OPMDs) and cancer. Furthermore, it is plausible that genetic predispositions within this population contribute to their heightened susceptibility to cancer development [39]. This suggests a multifactorial etiology, wherein both environmental exposures and inherent genetic susceptibilities synergistically influence disease

pathogenesis. This cytokine not only promotes tumor growth and invasion by stimulating angiogenesis and enhancing matrix metalloproteinases (MMPs) expression but also fosters an immunosuppressive milieu that aids in tumor evasion from immune surveillance. These findings underscore the intricate interplay between genetic factors, environmental exposures, and inflammatory processes in the initiation and progression of oral cancer.

According to studies conducted by Mio et al., the presence of acrolein and acetaldehyde in cigarette smoke can stimulate bronchial epithelial cells to produce higher levels of IL-8 [42]. Similarly, research by Huang et al. indicates that ethanol exposure can elevate plasma endotoxin levels and trigger the production of TNF-α and IL-1 [43]. These pro-inflammatory cytokines contribute to the augmentation of local and systemic IL-8 production in patients with alcoholic liver disease (ALD) [43]. In contrast to the marked increase observed in IL-1β levels, the rise in IL-8 levels appears to be less pronounced in this study. However, elucidating a direct correlation is complex. Sahibzada et al. demonstrated that various factors beyond exposure to risk factors can influence IL-8 levels, including lifestyle choices, geographical disparities, ethnic variations, genetic predispositions, and individual habits [44]. Moreover, findings from Vychaktami et al. suggest that certain dietary components commonly found in fruits and vegetables, such as curcumin, aloe vera, quercetin, and lycopene, possess anti-inflammatory properties and can inhibit the production of cytokines implicated in inflammation, including IL-1, IL-2, IL-6, IL-8, and IL-12 [45]. Consequently, it is plausible that the consumption of these dietary components may mitigate the elevation of IL-8 levels in individuals with risk factors [46]. This multifaceted interplay underscores the intricate mechanisms underlying cytokine regulation and the potential mitigating effects of dietary interventions on inflammation-associated pathways.

This study possesses several limitations that warrant acknowledgment. Firstly, the study did not account for the periodontal health status of participants, which may influence cytokine release in saliva. Secondly, the absence of information regarding the type of areca nut (unripe or overripe) utilized for betel nut chewing is pertinent, as it affects the alkaloid content in areca nut, potentially contributing to its carcinogenic properties. Additionally, the restricted saliva collection duration of 10 min may have led participants to inadvertently include mucoid substances in their samples, thereby impacting the assessment of salivary turbidity. Despite these limitations, the study's notable strength lies in being the first investigation of saliva profiles among individuals with oral cancer risk factors in East Indonesia, a region characterized by a high prevalence of such risk factors. As a recommendation for future research, it may be beneficial to include an evaluation of salivary antioxidants in relation to oral cancer susceptibility, thereby providing further insights into potential biomarkers for early detection and prevention strategies.

5. Conclusions

The present study uncovered differences in salivary IL-1β concentrations between individuals with and without habits linked to oral cancer risk. Nonetheless, no disparities were detected in salivary viscosity, color, turbidity, flow rate, acidity, or IL-8 levels. These findings suggest that alterations in salivary profiles may hold promise as early indicators and novel diagnostic tools for identifying abnormalities within the oral cavity.

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