## Journal information

# EUROPEAN JOURNAL OF MEDICAL RESEARCH

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Research website
ORCID profile
@MvanGriensven

Specialisms: **Regenerative medicine, Translational research, Musculoskeletal system**

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Research website
ORCID profile

Specialisms: **Oncology, Breast cancer**



## SECTION EDITORS

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**Section: Orthopaedics**

Research website
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Specialisms: **Gene therapy, mRNA, Bone healing, Biomaterials**

### Hossein Bannazadeh Baghi, PhD, Tabriz University of Medical Sciences, Iran

**Section: Infectious Diseases**



Research website
ORCID profile

Specialisms: **Viral disease, Viruses and human cancer, HPV, SARS-CoV-2/ COVID-19, Infectious diseases**

### Jia Cheng, MD PhD, Zhongshan Hospital of Xiamen University, China

**Section: Oncology**

Research website
ORCID profile

Specialisms: **Cancer, No-coding RNA, Epigenetic, Psychiatry**



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**Section: Neurology**



Research website

ORCID profile

Specialisms: **Parkinson's disease, Dystonia, Tremor, Clinical Neuropharmacology**

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**Section: Oncology**



Research website

Specialisms: **Oncology, Nephrology, Obstetrics and gynaecology, Reproductive health, Surgery, Oncologic surgery, Urology**

## Andrea De Vito, PhD, University of Sassari, Italy

**Section: Infectious Diseases**



Research website

ORCID profile

Specialisms: **HIV, STIs, Antiviral treatment, COVID-19, Antimicrobial therapy, Infectious diseases**

## Robert Ekart, MD PhD, University Medical Centre Maribor, Slovenia

**Section: Internal Medicine**



Research website
ORCID profile
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Specialisms: **Chronic kidney disease, Dialysis, Hypertension, Pulse wave velocity, Lung ultrasound, Kidney biopsy**

## Chengming Fan, MD, Central South University, China

**Section: Cardiology**



Research website
ORCID profile

Specialisms: **Human Induced Pluripotent Stem Cells, Cardiovascular Surgery, Heart Failure**

## Jochen Hinkelbein, MD DESA EDIC FASMA, Ruhr University Bochum, Germany

**Section: Intensive Care**



Research website
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Specialisms: **Emergency medicine, Intensive care medicine, Anaesthesiology**

## Radovan Hojs, MD, University Clinical Centre Maribor, Slovenia

**Section: Internal Medicine**

Research website
ORCID profile



Specialisms: **Nephrology, Dialysis, Cardiovascular morbidity, GFR**

## Bo Huang, PhD, Tongji Hospital, China

**Section: Obstetrics and Gynaecology**



Research website

ORCID profile

Specialisms: **Reproductive health, Embryobiology, Developmental biology**

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**Section: Dentistry**



Research website

ORCID profile

Specialisms:
**Periodontology, Oral Surgery, Oral Pathology, Dentistry**

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**Section: Surgery**



ORCID profile

Specialisms: **Surgical Gastroenterology, Minimal access surgery, General Surgery, Bariatric surgery**

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### Section: Public Health



Research website
ORCID profile

Specialisms: **Oncology, Cardiology, Rhythmic disorders, Medical genetics, Public health and prevention**

## Prasenjit Mitra, PhD, Institute of Post Graduate Medical Education and Research, India

### Section: Pathology



Research website
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@DrPrasenjit_Raj

Specialisms: **Clinical Chemistry, Laboratory Management, Molecular Psychiatry, Biomarkers, Toxicology**

## Gaurav Nepal, MD, Tribhuvan University, Nepal

### Section: Neurology



Research website
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@NepalGaurav_

Specialisms:
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## Roman Pfeifer, MD, University Hospital Zurich, Switzerland

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Research website

Specialisms: **Surgery, Orthopaedic Surgery, trauma surgery**

## ASSOCIATE EDITORS

## CARDIOLOGY

### Piotr Adamskii, MD PhD, Nicolaus Copernicus University, Poland



Research website
ORCID profile

Specialisms: **Cardiology, Electrophysiology, Arrhytmia ablations, Cardiac implantable devices, Acute coronary syndromes, Antiplatelet treatment, Randomized clinical trials, Pharmacokinetics, Pharmacodynamics**

### Pankaj Ahluwalia, MSc, PhD, Augusta University, USA



Research website
ORCID profile
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Specialisms: **Oncology, Genomics, Molecular profiling, Diagnosis, Tumor profiling, Whole genome sequencing, RNA sequencing, Non-coding RNA, Gene signature, Cancer, prognostic, Predictive, Biomarker, Gene expression, Transcriptomics, RNA, solid tumors, Colorectal cancer, Immunotherapy, Artificial intelligence.**

### Lamiaa Ahmed, PhD, Cairo University, Egypt

Research website
ORCID profile



Specialisms: **Pharmacology, Cardiovascular, nervous system, Stem cells**

## Hamed Akbari, MSc, Kerman University of Medical Sciences, Iran



Research website

ORCID profile

Specialisms: **Clinical Biochemistry, Diabetes, Cancer, Cardiovascular diseases**

## Derya Aydin Sahin, MD, Gaziantep University, Turkey

Research website

ORCID profile

Specialisms: **Pediatric cardiology, Invasive cardiology, Congenital heart disease, Asd, Vsd, Pda**

## Emanuele Bobbio, MD, Sahlgrenska University Hospital, Sweden



Research website

ORCID profile

Specialisms: **Heart failure, Cardiomyopathies, Myocarditis, Endomyocardial biopsy, Heart transplantation, Echocardiography, Cardiorenal syndrome**

## Jien Jiun Chen, MD, National Taiwan University Hospital, Taiwan

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Specialisms: **Cardiology, Electrophysiology, Sudden death, Catheter ablation**

## Hugo de Souza, PhD, Universidade de São Paulo, Brazil

Research website
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Specialisms: **Cardiovascular and metabolic diseases, Hypertension, Exercise physiology, Cardiopulmonary function test, Echocardiography, Heart rate variability analysis, Langendorff technique**

## Vikash Jaiswal, MD, Larkin Community Hospital, USA



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Specialisms: **Cardiology, Cardio-oncology, Internal medicine**

## Michal Laufer-Perl, MD MHA, Tel Aviv Sourasky Medical Center, Israel

ORCID profile

Specialisms: **Heart failure, Cardio-oncology, Echocardiography**

## Xiaoping Li, PhD, University of Electronic Science and Technology of China, China

Research website
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Specialisms: **Cardiomyopathy, Arrhythmia, Genetics**

## Giribabu Nelli, PhD, University of Malaya, Malaysia



Research website

Specialisms: **Cardiomyopathy, Heart failure, Bacterial infections, Drug therapy, Toxicology, Endocrinology and diabetes, Metabolism and metabolic disorders, Obesity, Reproductive endocrinology, Reproductive health**

## Valentina Nikolic, MD PhD, University of Nis, Serbia

Research website
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Specialisms: **Heart failure; Coronary artery disease; Clinical research; Translational research; Pharmacological treatment; Prediction model**

## Zach Rozenbaum, MD, Tulane University, USA

ORCID profile
@Rozenbaum_Z

Specialisms: **Interventional Cardiology, Structural Heart disease, Pulmonary Embolism**

## Marco Schiavone, MD, Luigi Sacco Hospital, Italy

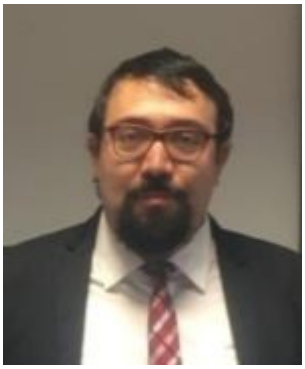
Research website
ORCID profile



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Specialisms: **Electrophysiology, Cardiac arrhythmias, Catheter ablation, Cardiac pacing, Cardiac devices, Atrial fibrillation, Ventricular tachycardia, Heart failure**

## Yusuf Ziya Şener, MD, Hacettepe University, Turkey



Research website
ORCID profile
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Specialisms:
**Cardiology, Intensive Care, Internal Medicine, HIV, Hemato-oncology, Nephrology, Rheumatology, Endocrinology**

## Jin-Yu Sun, MD, Nanjing Medical University, China



Research website
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Specialisms: **Cardiovascular disease, Hypertension, Heart failure, Cardio-oncology, Obesity, Oncology, Biomarkers, Machine learning, Prediction model**

## Takeshi Tsuda, MD, Nemours Children's Health System, USA

ORCID profile

Specialisms: **Congenital heart disease, Pediatric cardiology, Cardiomyopathy, Muscular dystrophy, Exercise physiology, Cardiopulmonary exercise testing,**

**Heart failure, Cardiovascular development, Sudden cardiac death, Cardio-oncology, Extracellular matrix, Signal transduction**

## Chuan Wang, MD PhD, Beijing Anzhen Hospital, China



Research website
ORCID profile

Specialisms: **Cardiac disease, Cardiac surgery, Coronary artery bypass grafting, Randomized controlled trial, Meta-analysis, review, Regression, Survival analysis**

## Yucong Zhang, PhD, Hua Zhong University of Science and Technology, China



Research website
ORCID profile

Specialisms: **Urology, Andrology, Geriatrics, Cardiology, Epidemiology**

## Lei Zhao, MD, Capital Medical University, China

Research website
ORCID profile

Specialisms: **Cardiology, Heart failure, Myocardial infarction, ACS, Epicardial adipose tissue, Metabolic syndrome**

## Xiang Zhou, PhD, Soochow University, China



ORCID profile

Specialisms: **Atherosclerosis, Cardiovascular disease, Metabolic disease**

## Youfeng Zhu, MD PhD, Jinan University, China



Research website

ORCID profile

Specialisms: **Sepsis, Critical care medicine, Heart failure, Mechanical ventilation, Sepsis-induced cardiomyopathy**

---

# DENTISTRY

## Romeo Patinii, DDS PhD, Università Cattolica del Sacro Cuore, Italy



Research website

ORCID profile

Specialisms: **Oral microbiota, Oral diseases, Systematic reviews**

## Alessandro Polizzi, DDS, University of Catania, Italy

Research website

ORCID profile

Specialisms: **Orthodontics, Oral surgery, Periodontology and on the clinical and molecular aspects of Oral Diseases**



## Keunbada Son, PhD, Kyungpook National University, South Korea



Research website

ORCID profile

Specialisms: **Dentistry, Digital Dentistry, Prosthodontics, Dental CAD/CAM Systems, Learning Effect**

# INFECTIOUS DISEASES

## Javeed Ahmad, PhD, National Institutes of Health, USA



Research website

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Specialisms: **Infectious diseases, Virology, Nanobodies and structural immunology**

## Yanfei Chen, PhD, Zhejiang University, China



Research website

ORCID profile

Specialisms: **Infectious disease, Intestinal microbiota, Liver diseases, Liver failure, Viral Autoimmune hepatitis, Primary biliary cholangitis**

## Mümtaz Güran, PhD, Eastern Mediterranean University, Turkey

ORCID profile

Specialisms:
**Antimicrobial susceptibility testing, Antibiotic resistance, Antimicrobials, General microbiology**

## Shafiul Haque, PhD, Jazan University, Saudi Arabia



Research website
ORCID profile

Specialisms: **Microbiology, Biochemistry, Molecular biology, Genetics, Bioinformatics**

## Yi-Ping Li, PhD, Sun Yat-sen University, China



Research website
ORCID profile

Specialisms: **Antibiotics; Antiviral treatment; Viral diseases; Drug resistance; Viral hepatitis; Vector-borne disease**

## Carsten Münk, PhD, University of Düsseldorf, Germany

Research website
ORCID profile

Specialisms: **Virology, Innate Immunity**

## Seyed Aria Nejadghaderi, MD, Shahid Beheshti University of Medical Sciences, Iran

Research website
ORCID profile



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Specialisms: **Global burden of disease, Non-communicable diseases, Epidemiology, Oncology, Infectious diseases, COVID-19, Risk factors, Public health, Systematic review, Meta-analysis**

## Shi Zhao, PhD, Chinese University of Hong Kong, Hong Kong



Research website
ORCID profile

Specialisms: **Zoonotic and emerging infections, Vaccines, Public health and prevention**

## Changtai Zhu, PhD, Shanghai Sixth People's Hospital, China



Research website
ORCID profile

Specialisms:
**Haematology, Bacterial infections, Drug resistance, Public health and prevention**

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# INTENSIVE CARE

## Ahmed Hosny Hassan,Pharm D, MD, Mansoura University Hospital, Egypt

Research website
ORCID Profile
@AhmedHosny02

Specialisms: **Infectious diseases, Clinical nutrition, Pharmacotherapy, Clinical pharmacology, Therapeutics, Clinical pharmacy, Pharmacy practice, Clinical trials, Clinical research**

## Paolo Formenti, MD, Ospedale Bassini, Italy

Research website

Specialisms:
**Anaesthesiology, Emergency medicine and critical care, Pulmonary medicine, Pharmacological treatment, Meta-analysis, Statistics, Systematic reviews**

## Ramakanth Pata, MD, University of Cincinnati Medical Center, USA



Research website
ORCID profile

Specialisms: **ARDS, Septic Shock**

## Valery Piacherski, PhD, Mogilev State A.Kuleshov University, Belarus



Research website
ORCID profile

Specialisms:
**Anesthesiology, Intensive care, Regional anesthesia, Peripheral nerve blocks**

## Jay Prakash, MD PhD MBBS DNB FCCS, Rajendra Institute of Medical Sciences, India



Research website
ORCID profile

Specialisms:
**Emergency medicine and Critical care; Cardiology; infectious diseases; Anaesthesiology; Endocrinology and diabetes; Gastro-oesophageal reflux disease; GI bleeding; Inflammatory bowel disease; Liver cirrhosis; Pancreatitis; Peptic ulcer; General internal medicine; Haematology;**

## Guo-Wei Tu, MD, Fudan University, China



Research website
ORCID profile

Specialisms: **Intensive care medicine, Critical care, Hemodynamic monitoring, Heart failure, Sepsis, Shock, ARDS**

## Zhanqi Zhao, MD PhD, Furtwangen University, Germany



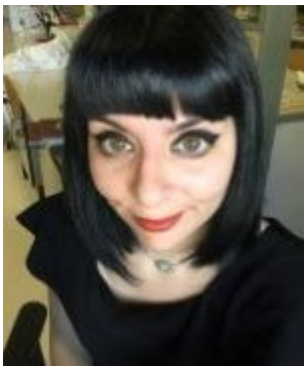
Research website
ORCID profile

Specialisms: **Medical imaging, Clinical application of novel medical devices, Mechanical ventilation in intensive care unit, Ventilator-induced lung injury, Thorax applications of electrical impedance tomography, Pulmonary function test**

---

# INTERNAL MEDICINE

## Giulia Angelini, MD PhD, Università Cattolica del Sacro Cuore, Italy



Research website

ORCID profile

Specialisms: **Type 2 Diabetes, Obesity, NAFLD, NASH, Bariatric Surgery, Molecular Biology**

## Fateen Ata, MD, Hamad Medical Corporation, Qatar



Research Website

ORCID Profile

Specialisms: **Endocrinology and diabetes, Internal medicine, Pulmonary Embolism**

## Changchun Cao, MD PhD, Nanjing Medical University, China

Research Website

ORCID Profile

Specialisms: **Acute kidney injury**

## Hao Chen, MD, Yokohama City University, Japan

Research website

ORCID profile

Specialisms: **Oncology, Pulmonary diseases, Infection, Clinical research, Meta-analysis**

## Hassan Choudry, MBBS, University of Leicester, UK



Research website

ORCID profile

Specialisms: **Rhythmic disorders, Gastroenterology and hepatology, Public health and prevention**

## Gopal Krishna Dhali, MBBS MPH, Nottingham University Hospitals NHS Trust, United Kingdom



Research website

ORCID profile

Specialisms: **Chronic pancreatitis, Inflammatory bowel disease, Irritable bowel syndrome**

## Lin Fan, MD, Tongji University, China

Research website

ORCID profile

Specialisms: **Diagnosis or treatment study on tuberculosis, Clinical immunology study on tuberculosis, Drug resistant TB, Novel diagnostic study concerning biomarkers distinguishing active TB from non-TB diseases and latent TB infection, Novel Clinical trial on TB treatment.**

## Alessandro Granito, PhD, University of Bologna, Italy

Research website

ORCID profile

Specialisms:

**Immunology and allergy, Oncology, Tumours, Liver cancer, Rheumatology and**



**musculoskeletal disorders**

## Stefano Guarino, MD PhD, University of Campania "Luigi Vanvitelli", Italy



Research website

Specialisms: **Nephrology; Chronic kidney disease; Hypertension; Renal calculi**

## Timotius Ivan Hariyanto, MD, Pelita Harapan University, Indonesia



Research Website

ORCID Profile

Specialisms: **Endocrinology, Diabetes, Metabolic disorders, Obesity, Thyroid, Viral infection, Antiviral treatment, Tropical disease, Hypertension, Systematic review, Meta-analysis, Clinical studies**

## Wandong Hong, PhD, First Affiliated Hospital of Wenzhou Medical University, China



Research website

ORCID profile

Specialisms: **Acute pancreatitis, Peptic ulcer, Therapeutic endoscopy, Liver cirrhosis, GI bleeding**

## Mohammad-Salar Hosseini,MD MPH, Tabriz University of Medical Sciences, Iran



Research website
ORCID profile

Specialisms: **Internal medicine, Evidence-based medicine, Oncology, Immuno-oncology, Gastroenterology, Public health**

## Aleksandra Klisic, MD PhD, University of Montenegro, Montenegro



Research website
ORCID profile

Specialisms:
**Endocrinology and diabetes, Metabolism and metabolic disorders, Obesity, Hypertension, Geriatrics and aged care, Gastroenterology and hepatology, Inflammation, Biomarkers, Medical biochemistry, Public health and prevention**

## Arunkumar Krishnan, MD, Atrium Health Wake Forest Baptist, USA



Research website
ORCID profile

Specialisms:
**Endocrinology and diabetes, Gastroenterology and hepatology, Obesity, Hepatobiliary diseases, Liver disease**

## Wei Leii, MD PhD, First Affiliated Hospital of Soochow University, China

ORCID Profile



Specialisms: **Asthma**

## Panita Limpawattana, MD, Khon Kaen University, Thailand



Research website

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Specialisms: **Geriatrics and aged care, Dementia**

## Ahmet Murt, MD, Istanbul University-Cerrahpasa, Turkey



Research website

ORCID profile

Specialisms: **Nephrology, Kidney transplantation, Glomerulonephritis, Hemodialysis, Peritoneal dialysis, Immunology**

## Venkata Suresh Patthipati, MD, Sound Physicians, USA



Research website

ORCID profile

Specialisms: **Internal Medicine, Gastroenterology, Pulmonary critical care, Biostatistics**

## Vivek Podder, MBBS, Baptist Health South Florida, Bangladesh

Research website

ORCID profile

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Specialisms:
**Cardiology, Diabetes, Neurology, Public health and Prevention, Rheumatology and musculoskeletal disorders**

## Jeffrey Pradeep Raj, MD MBBS, King Edward Memorial Hospital and Seth G.S. Medical College, India

Research website
ORCID profile

Specialisms: **General internal medicine, Family medicine, Biostatistics, Clinical trials, Clinical research, Research methodology, Clinical pharmacology, Pharmacology**

## Kassem Sharif, MD, Sheba Medical Center, Israel



Research website

Specialisms:
**Gastroenterology and hepatology, Rheumatology and musculoskeletal disorders**

## Paolo Usai-Satta, MD, Azienda Ospedaliera G. Brotzu, Italy

Research website
ORCID profile

Specialisms: **Gastroenterology and Hepatology; Gastro-oesophageal Reflux disease; Clinical research; Pharmacological treatment; diagnosis; Prospective studies; Retrospective studies;**

## Deguang Wang, MD, Second Hospital of Anhui Medical University, China

Research website
ORCID profile

Specialisms: **Nephrology, Acute kidney injury, Chronic kidney disease, Epidemiology, Fibrosis, Inflammation, Machine learning, Mendelian randomization**

## Tobias Weismüller, MD, Vivantes Klinikum, Germany



Research website
ORCID profile

Specialisms: **Hepatobiliary diseases, Autoimmune liver disease, Interventional endoscopy, Liver transplantation**

## Dongshan Zhang, MD, Central South University, China

Research website
ORCID profile

Specialisms: **Acute kidney injury, Renal fibrosis**

## Pan Zhao, MD PhD, Chinese PLA General Hospital, China



Research website

Specialisms:
**Hepatology, Viral Hepatitis, Liver Injury, Genetic Liver Diseases**

## Zijing Zhou, MD PhD, Central South University, China



Research website

ORCID profile

Specialisms: **Pulmonary fibrosis, Stiffness, Extracellular matrix, COPD**

## NEUROLOGY

### Ehsan Alimohammadi, MD, Kermanshah University of Medical Sciences, Iran

Research Website

ORCID profile

Specialisms: **Neurosurgery, Neurooncology, Spine, Traumatic brain injury, Skull base surgery**

### Yimin Chen, MD, Foshan Second People's Hospital, China



ORCID profile

Specialisms:
**Neurology, Endovascular Thrombectomy, Cerebrovascular Disease, Neuroimmunity, Psychology**

### Yi Chao Foong, MBBS, Monash University, Australia

ORCID profile

Specialisms: **Multiple sclerosis, Digital biomarkers, Healthy ageing, Smartphone apps**

## Petr Kanovsky, MD PhD, Palacký University, Olomouc, Czech Republic

Research Website
ORCID profile

Specialisms: **Neuroinflamation and neurodegeneration, Biomarkers of neurodegeneration, Central mechanism of dystonia, Botulinum toxin treatment**

## Chaeyoung Lee, PhD, Soongsil University, South Korea



Research Website
ORCID profile

Specialisms: **Vascular dementia, Genomics, eQTL, Omics, Mixed model**

## Hamza Maqsood, MD, Nishtar Medical College and Hospital, Pakistan



Research website
ORCID profile

Specialisms: **Neurology**

## Luca Marsili, MD PhD, University of Cincinnati, USA

Research Website
ORCID profile

Specialisms: **Movement disorders, Parkinson's disease, Parkinsonism, Genetics, Neurophysiology, Dystonia, Neurodegeneration, Wearable sensors**

## Mohammad Mofatteh, PhD MPH, Queen's University Belfast, United Kingdom



Research Website
ORCID profile
@DrMofatteh

Specialisms: **Neurosurgery, Awake craniotomy, Tumor, Glioma, Glioblastoma, Oncology, Deep brain stimulation, Neurodegeneration, Alzheimer, Parkinson, Cerebrovascular, Neurology, Stroke, Traumatic brain injury, Spine, Spinal cord injury, Depression, Anxiety, Patient outcome, Artificial intelligence, Augmented reality, Virtual reality**

## Vrutangkumar Shah, PhD, Oregon Health & Science University, USA



Research website
ORCID profile

Specialisms: **Digital Medicine, Gait and Balance Disorders, Wearable Sensors, Machine Learning, Movement Disorders**

## Anwen Shao, MD PhD, Zhejiang University, China



Research website

Specialisms: **Stroke, Neurointensive care, Neurosurgery**

## Mudit Tyagi, PhD, Thomas Jefferson University, USA

Research website
ORCID profile



Specialisms: **Dementia; Neurodegenerative disease; Neuroinfection; Vascular disease; Antiviral treatment; HIV/AIDS; Viral diseases; Basic research; Experimental research;**

### Yuzhen Xuu, MD PhD, Shandong First Medical University, China



Research website
ORCID profile

Specialisms: **Neurology, Neuroscience, Stroke, Rehabilitation, Dementia, Cognitive, Diabetes, Complementary and alternative medicine, Translational medicine**

## OBSTETRICS & GYNAECOLOGY

### Shima Alizadeh, MD, Tehran University of Medical Science, Iran



### Xiang Hong, PhD, Southeast University, China



Research website
ORCID profile

Specialisms: **Obstetrics and gynaecology, Endocrinology and diabetes, General practice and family medicine, Infectious diseases, Public health and prevention**

## ONCOLOGY

## Mahdi Abdoli Shadbad, PhD, Tabriz University of Medical Sciences, Iran



Research website

ORCID

Specialisms: **Cancer, Immunotherapy, System biology**

## Asis Bala, PhD, Institute of Advanced Study in Science and Technology, India



Research website

ORCID profile

Specialisms: **Breast Cancer; Chemo-resistance; Chemotherapy; Tumor Biology; Endocrinology; Immunology; Molecular Pharmacology; Immune Therapy**

## ZhenCong Chen, MD, Fudan University, China



Research website

Specialisms: **Sarcoma, Chemotherapy, Tumours, Myeloma, Oncologic surgery**

## Quan Cheng, MD, Central South University, China



Research website

ORCID profile

Specialisms: **Bioinformatics, Medical genetics, Neurosurgery, Chemotherapy, Tumors**

## Peixin Dong, MD PhD, Hokkaido University, Japan

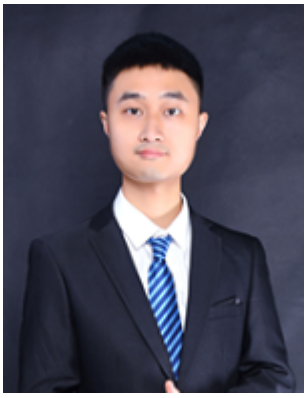


Research website

ORCID profile

Specialisms: **Oncology, Epigenetics, Chemoresistance, Gene, Non-coding RNA, EMT, Cancer stem cells, CRISPR genome editing, Tumor microenvironment, Cancer bioinformatics, Resistance to targeted therapies, Biomarkers, Cell biology, Clinical trials, Internal medicine, Drug discovery and drug development**

## Dechao Feng, PhD, West China Hospital of Sichuan University, China



Research website

ORCID profile

Specialisms: **Geriatrics and aged care, Immunology and allergy, Medical genetics, Tumours, Urology**

## Mihnea-Alexandru Găman, MD, Institutul Clinic Fundeni, Romania



Research website

ORCID profile

Specialisms: **Hematology**

## Ping Han, MD, West China Hospital of Sichuan University, China

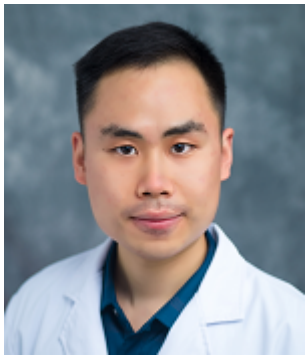
Research website

ORCID profile



Specialisms: **Geriatrics and aged care, Immunology and allergy, Medical genetics, Tumours, Urology**

## Lei Huang, PhD, Shanghai Jiao Tong University, China



Research website

ORCID profile

Specialisms: **Cancer epidemiology, Precision oncology, Translational oncology, Clinical oncology, Surgery**

## Zhengwei Huang, PhD, Jinan University, China



Research website

Specialisms: **Drug development, Chemotherapy**

## Qi Jia, MD, Shanghai Changzheng Hospital, China



Research website

ORCID profile

Specialisms: **Sarcoma, Chordoma, Giant cell tumor, Bone tumor, Metastatic bone tumor, Spine, Spine surgery, Orthopedic, neurosurgery**

## Feng Jiang, MD, Fudan University, China

Research website

ORCID profile



Specialisms: **Bioinformatics, Machine learning, Cancer biology, Data mining**

## Xuefeng Kan, PhD, Tongji Hospital, China

ORCID profile

## Nobuyuki Koyama, MD PhD, Saitama Medical University, Japan

Research website

ORCID profile

Specialisms: **Pulmonology, Oncology**

## Sanjay Kumar, PhD, Sharda University, India

Research website

ORCID profile

Specialisms: **Extracellular vesicles, Exosomes, Multiple Myeloma, Breast Cancer, Kidney disease, Evaluation of differentially expressed genes, Molecular Docking MD Simulation, MMGBSA, PCA Analysis**

## Dongjun Lee, PhD, Pusan National University, South Korea

Research website

ORCID profile

Specialisms: **Hematology-oncology, Stem cell, Vascular disease, Haematology, Hematological malignancy, Immunity, Inflammation, Cell death, Cell differentiation, Disease models**



## Jitian Li, PhD, Luoyang Orthopedic-Traumatological Hospital of Henan Province, China



Research website

ORCID profile

Specialisms: **Oncology, Orthopedics, Proteomics**

## Kai Li, PhD, Harbin Institute of Technology, China



Research website

ORCID profil

Specialisms: **Oncology, Chemotherapy, Tumours, Immunology and allergy**

## Chao Liu, MD PhD, Shandong Tumor Hospital, China



Research website

ORCID profile

Specialisms: **Cancer radiotherapy, Chemotherapy, Immunotherapy, Single cell sequencing, Immunology, Biomarker**

## Hongda Liu, MD PhD, Jiangsu Province Hospital, China

Research website

ORCID profile



Specialisms: **Gastroenterology and hepatology, Medical genetics, Tumours, Oncologic Surgery**

## Jinhui Liu, MD PhD, Jiangsu Province Hospital, China



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Specialisms: **Obstetrics and gynaecology, Oncology, Medical genetics, Bioinformatics, Machine learning**

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Specialisms: **Urologic Neoplasms, Kidney Neoplasms, Urinary Bladder Neoplasms, Prostatic Neoplasms, Prognosis, New Application of Therapies, Meta-analysis, Diagnosis, Outcomes, Retrospective Studies, Oncologic Surgery, Precision Oncology, Urological Surgery**

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Specialisms: **Gastroenterology and hepatology, Chemotherapy, Tumours**

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Specialisms: **Oncology, Molecular genetics, Anti-cancer drugs, Non-coding RNA**

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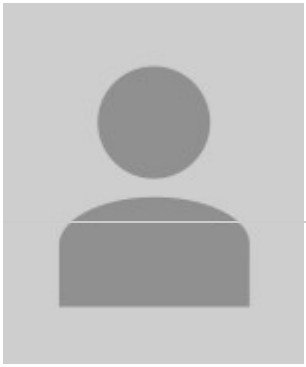
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**Geriatrics, Prevalence**

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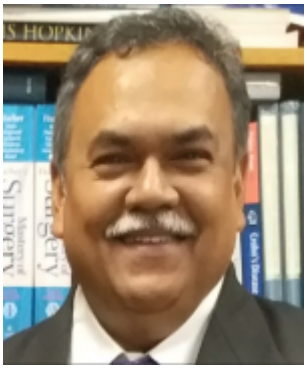


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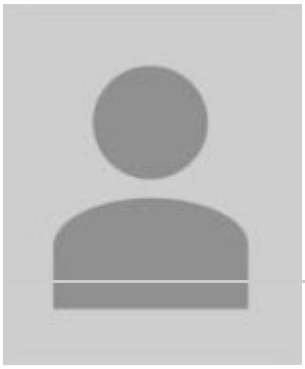
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Gezer *et al.*
*European Journal of Medical Research* (2024) 29:64
https://doi.org/10.1186/s40001-024-01654-5

European Journal of Medical Research

RESEARCH Open Access

# *N*-Nitrosomorpholine-induced oncocytic transformation in rat endocrine organs

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## Abstract

**Background** *N*-Nitrosomorpholine (NMO) is one of the most common *N*-nitroso compounds. An oncocytic transformation has been demonstrated in renal tubules of NMO-treated rats. In our study, we aimed to investigate the potential transformation of oncocytic cells in 6 endocrine organs, i.e., thyroid, adrenal and pituitary glands, pancreas, testis, and bone, of NMO-exposed rats.

**Methods** Thirty male rats were born and raised. Fifteen of them were given a single dose of 320 mg NMO per kg body weight, dissolved in drinking water, by a gavage tube. At the end of 52 weeks, the animals in both series were killed. Right after the killing, 6 different endocrine organs (hypophysis, thyroid, pancreas, adrenal gland, bone [femur], and testicles) of each animal were excised.

**Results** There was no evidence of oncocytic cell development in the control group. In contrast, oncocytes were observed in 8 out of 13 NMO-treated rats: 2 in the adrenal sections, 1 in the thyroid sections, 3 in the pituitary sections, and 2 in the pancreas sections. Thesticle and bone sections were completely normal.

**Conclusions** We showed that NMO induced an oncocytic change in pancreas, thyroid, pituitary, and adrenal glands. To date, no identified specific environmental risk factors that lead to an oncocytic transformation in endocrine glands have been reported previously. Given the increasing prevalence of endocrine-disrupting chemicals in the environment, personal care products, manufactured goods, and food sources, there is a need to advance our understanding of the pathological mechanisms underlying oncocytosis in endocrine organs.

**Keywords** Nitroso compounds, Oncocyte, Endocrine disrupting chemical, Endocrine disruptors, Endocrine gland neoplasms

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## Background

*N*-Nitroso compounds have become a potentially large source of exposure for human beings to chemical carcinogens in the recent years. *N*-Nitrosomorpholine (NMO) is one of the most common *N*-nitroso compounds, which has been frequently detected in the discharged water from sewage treatment plants, some cosmetics and toiletries, fine-cut chewing tobacco used for snuff-dipping and as an air pollutant in regions where tire-manufacturing and rubber factories are located [1–4]. This tumorigenic compound has been shown previously to be mainly hepatotoxic, inducing hepatocellular carcinoma

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[5, 6]. Moreover, NMO also triggered the development of neoplasms in the respiratory and upper digestive tracts, thyroid gland, brain, and spleen in various animal experiments [7–10].

An oncocyte is an enlarged cell with abundant eosinophilic, granular cytoplasm, in which a large hyperchromatic nucleus exists [11]. This oncocytic change is caused by proliferation and accumulation of mitochondria within the cell, and it has been mainly attributed to the alterations related to the mitochondrial DNA [12]. These mitochondrial anomalies are triggered by chronic inflammation secondary to aging or various chemical carcinogens such as NMO [13–15]. Various studies have demonstrated an oncocytic transformation in renal tubules of NMO-treated rats [15–20]. In addition to that, germline mutations of the *Gene associated with Retinoid-Interferon-induced Mortality (GRIM)-19* have also been indicated as a possible etiological factor in the development of an oncocytic tumor [21]. This metaplastic differentiation has been observed in various organs, such as thyroid, parathyroid, pituitary and adrenal glands, pancreas, kidney and paraganglia [13]. In our study, we aimed to investigate the potential transformation of oncocytic cells in six endocrine organs, i.e., thyroid, adrenal and pituitary glands, pancreas, testis, and bone, of NMO-exposed rats.

## Materials and methods

### Characterization of N-nitrosomorpholine (NMO)

NMO was provided from MedChemExpress, New Jersey, USA; via a distributor located in our region, named Suarge Biotechnology Co., Ltd., Istanbul, Turkey. The purity and solubility of NMO were reported as 98.22% and ≥ 100 mg/mL at 19 ℃, respectively. The appearance was solid < 29 ℃ and liquid ≥ 29 ℃. The chemical could be stored at 4 ℃ for 2 years. It was also reported that NMO was light-sensitive and could be stable at room temperature for more than 14 days in neutral form in dark.

### Animal experiments

Thirty male Sprague–Dawley rats (about 8-week old) weighing about 200 g were born and raised in the Experimental Medicine Research and Application Unit of our institution. Fifteen rats were given a single dose of 320 mg NMO per kg body weight, dissolved in drinking water, by a gavage tube. The amount of this chemical agent was determined according to a previously reported rat study, in which a single dose of 320 mg/kg NMO was administered to the animals [20]. The animals were placed in different cages in groups of 5 and maintained under constant conditions (20 ± 2 C and 12 h light/dark cycle). The rest 15 rats, used as controls, were also administered placebo by gavage in the same day and housed in groups of 5 in the same room with the others. Afterward, the rats were kept on a standard laboratory diet and tap water for 52 weeks (*ad-libitum*).

The maintenance period from the start of the experiment to the killing was based on various rat studies which revealed data on the time of appearance and incidence of oncocytic lesions [10, 14, 17, 18]. Laboratory animals were cared for and fed in Eurostandard type IV cages (1354G EUROSTANDARD TYPE IV 598 × 380 × 200 mm, floor area: 1820 $cm^2$) defined under the condition of "management and implementation instructions for the breeding and protection of animals used for experimental and other scientific parts". Only health monitoring protocol was to make a daily inspection of rats' behavior and record in case of any abnormality. No abnormal behavior was observed, even in the rats which were deceased during the experiment. In addition to that, observation of daily food and water consumption of the rats was made and no differentiation of any rat's consumption from the others was observed.

At the end of 52 weeks, the animals in both series were killed using xylazine and ketamine intraperitoneal injections. All rats were killed between 9 a.m. and 1 p.m. in 2 consecutive days; NMO-treated group in the first day and controls in the second day. The main reason to kill 2 groups in 2 consecutive days within the similar daytime period was to control for the circadian rhythm differences between the groups. Right after the killing, six different endocrine organs (hypophysis, thyroid, pancreas, adrenal gland, bone [femur], and testicles) of each animal were excised. The only excluding criterion in this study was the development of mortality during the experiment.

### Histopathological examination

Each organ was stored rapidly in a plastic sterile container full of 10% formaldehyde solution. Thereafter, tissue samples taken from the removed organs were fixed and embedded in paraffin for light microscopic examinations. Each of the organs was examined by serial sectioning. Section thicknesses were 3 μm. Nine separate sections were made for each organ. The histological sections were stained with hematoxylin and eosin (H&E). The presence of oncocytic cells in each tissue section was investigated under the microscope by two pathologists. The 1st, $5^{th}$, and 9th sections were examined. Presence of any oncocytic cell was expressed as percentage. The average of the oncocytic cell percentages in these three sections for each organ was

recorded as the oncocytic cell percentage specific to that organ.

## Results

### Mortality data

A total of three rats, two from the carcinogen-treated group and one from controls, were found deceased within this period, by the weeks 44, 50, and 48, respectively, after the beginning of the experiment, respectively. Diagnostic necropsy examinations of the deceased rats revealed normal postmortem changes; thus, no additional examination was performed.

### Histopathological outcome

Six endocrine organs (hypophysis, thyroid, pancreas, adrenal gland, bone, and testicles) of 27 rats (13 NMO-treated and 14 controls) were evaluated in a total of 162 H&E stained sections.

There was no evidence of oncocytic cell development in the control group. In contrast, oncocytes were observed in 8 out of 13 NMO-treated rats: 2 in the adrenal sections (Fig. 1), 1 in the thyroid sections (Fig. 2), 3 in the pituitary sections (Fig. 3), and 2 in the pancreas sections (Fig. 4).

Interestingly, of these 8 animals, each one developed oncocytic transformation in only one organ. The percentages of the oncocytes in the sections are described in detail in Table 1. The cells in the testicle and bone sections were completely normal, with no oncocytic appearance.

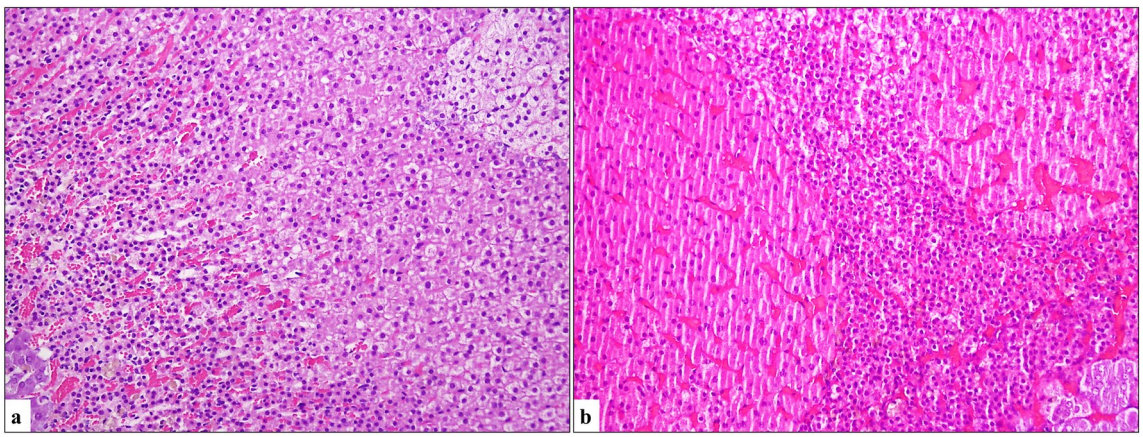



**Fig. 1** **a** Normal adrenal gland layers (inner to outer layer) (H&E, × 200). **b** Oncocytic cell groups with well-defined cell borders, deeply eosinophilic, granular cytoplasm, small round nuclei (H&E, × 200)

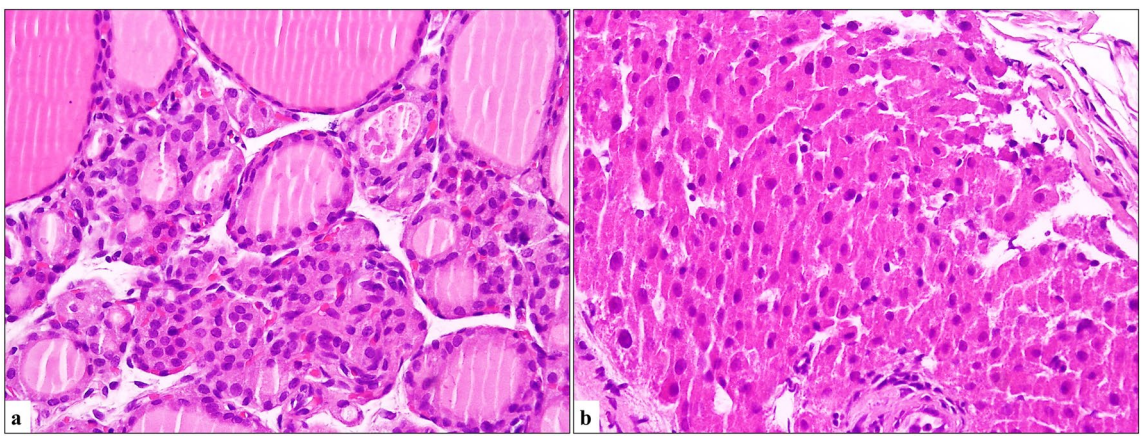



**Fig. 2** **a** Thyroid parenchyma composed of normal follicle epithelial cells (H&E, × 400). **b** Oncocytes with large size, prominent cell borders, eosinophilic, and granular cytoplasm on thyroid sections (H&E, × 400)

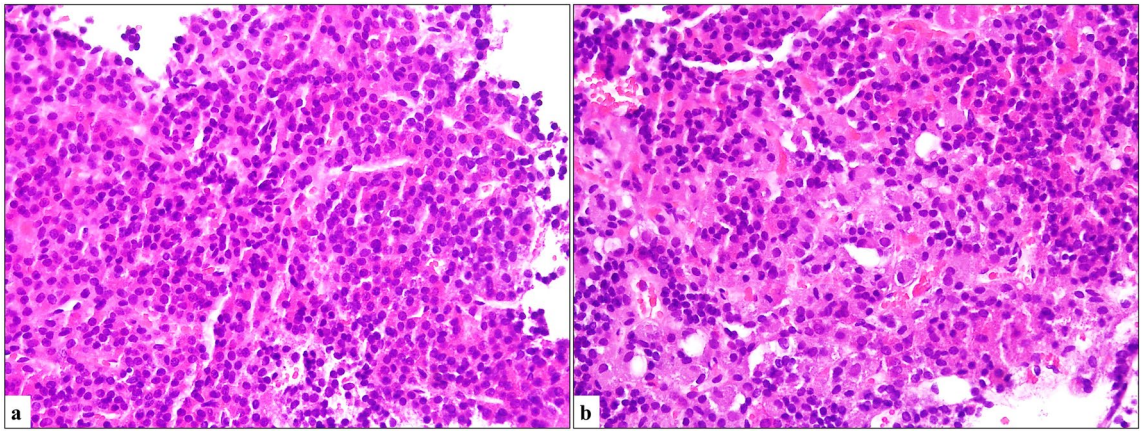



**Fig. 3** **a** Normal pituitary tissue showing relative cellular monomorphism with a single cell type (H&E, ×400). **b** Oncocytic cells scattered in the pituitary parenchyma (H&E, ×400)

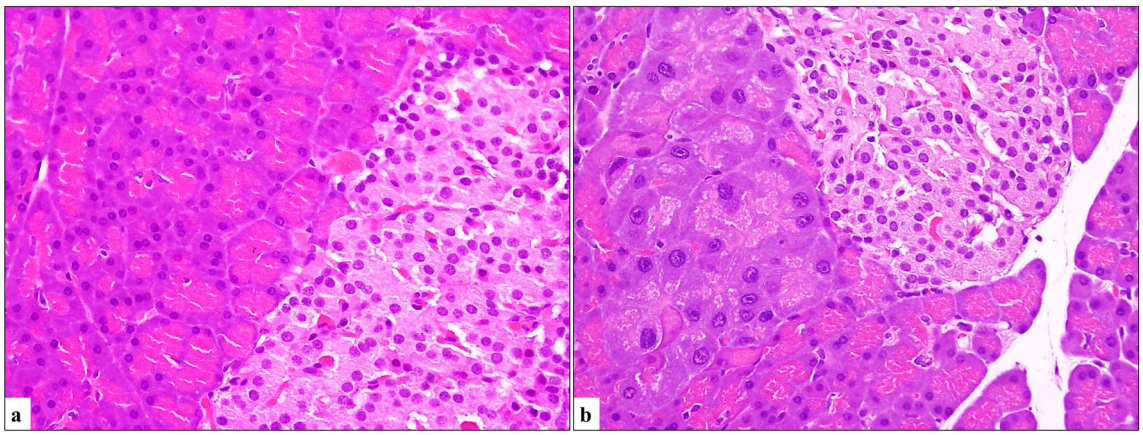



**Fig. 4** **a** Normal pancreatic parenchyma (H&E, ×400). **b** Oncocytic cells located between acinar cells and endocrine cells (H&E, ×400)

**Table 1** The percentages of oncocytic cells in the sections of the endocrine organs of the NMO-treated rats

| Rat # | Percentages of oncocytes | | | | | |
|---|---|---|---|---|---|---|
| | Adrenal | Thyroid | Pituitary | Pancreas | Bone | Testis |
| 1 | 10 | – | – | – | – | – |
| 2 | 10 | – | – | – | – | – |
| 3 | – | – | – | – | – | – |
| 4 | – | – | – | – | – | – |
| 5 | – | – | 10 | – | – | – |
| 6 | – | – | 20 | – | – | – |
| 7 | – | – | – | – | – | – |
| 8 | – | – | – | 5 | – | – |
| 9 | – | – | – | 5 | – | – |
| 10 | – | 20 | – | – | – | – |
| 11 | – | – | 10 | – | – | – |
| 12 | – | – | – | – | – | – |
| 13 | – | – | – | – | – | – |

## Discussion

The results of the present study showed that NMO is a chemical compound which induces oncocytic transformation in the rat endocrine organs, i.e., adrenal, thyroid and pituitary glands, and pancreas. To date, in terms of oncocytic change, rat kidney has been the only proven organ which developed oncocytic tubules and oncocytoma after exposure to NMO in various animal studies. Similar to the methods of our study, Nogueira et al. administered single doses of 320 mg/kg of NMO by a gavage tube to a group of rats and started killing the rats 50 weeks after the start of the experiment [20]. Besides this group, three other groups of rats were given NMO in single doses of 200 mg per body weight dissolved in the drinking water at concentrations of 50 mg/100 ml or 20 mg/100 ml for 7 or 3 weeks. By the week 50 after the start of NMO administration, renal clear cell tumors and/or tubules were most frequently observed in the group which was treated with 320 mg of NMO per body weight and the authors reported that the granular acidophilic cells with larger central nuclei were more prevalent than clear cell lesions in all sections. Previous studies reported the appearance of oncocytic renal tubules after 15 and 23 weeks' exposure to NMO [15, 16]. In our study, we aimed to increase the likelihood of developing oncocytic lesions in the endocrine organs by maintaining the rats for 52 weeks.

The cytoplasm of an oncocyte is described as "swollen" which is due to mainly the presence of numerous abnormal mitochondria in the cellular cytoplasm [22, 23]. The main mechanism for this granular, large, and eosinophilic cytoplasm filled with mitochondria has been indicated as the impairments in the mitochondrial DNA, which is supposed to be more susceptible than nuclear DNA to environmental carcinogens [12]. The accumulation of mitochondria has been attributed to the compensatory mechanism following exposure to toxic substances.

In our study, pituitary gland was clearly the most affected endocrine gland by the administration of NMO, in terms of oncocytic transformation. The well-vascularization of pituitary gland by the hypothalamohypophyseal portal system may be a possible explanation for this outcome, by making the gland tissue more sensitive to the environmental endocrine disruptors [24]. Oncocytic change has been mainly demonstrated in gonadotroph adenomas. A hundred cases with gonadotroph adenomas were analyzed by Young et al. and a patchy acidophilic appearance corresponding to oncocytic change was reported for most of the specimens [25]. In another study, oncocytic adenomas were described as clinically inactive pituitary adenomas, together with null cell adenomas and gonadotroph adenomas [26]. In short, the asymptomatic nature of oncocytic pituitary adenomas may cause an underestimation of the actual prevalence of pituitary adenomas with oncocytic features, especially for the areas with elevated *N*-nitroso compounds in the air and/or drinking water.

Oncocytic transformation is not an uncommon pathological finding in both benign and malignant thyroid lesions. In a recent review, the oncocytic change in thyroid pathology has been discussed in detail and it has been described in thyroiditis, thyroid follicular adenomas, follicular-patterned differentiated thyroid carcinomas, papillary carcinomas, poorly differentiated carcinomas, and medullary thyroid carcinomas [13]. In line with the literature, our study demonstrated that NMO, a tumorigenic chemical, induced an oncocytic transformation in the thyroid tissue of one rat with a high percentage (20%) of oncocytes.

In various reviews and case reports, oncocytic neoplasms have been described for both adrenal gland and pancreas [27–30]. Intraductal oncocytic papillary neoplasms (IOPNs), the precursor lesions of invasive carcinoma, are generally cystic neoplasms, which may cause pancreatic ductal obstruction. In contrast, oncocytic neoplasms arising in the adrenal glands are mostly benign and nonfunctional tumors, which rarely transform to oncocytic adrenocortical carcinoma. There are limited data on genetic mutations in IOPNs and adrenal oncocytic neoplasms. In the present study, oncocytes were observed in the adrenal glands of two rats and in the pancreas tissues from another two rats with relatively low percentages of oncocytes (5%) compared to the adrenal glands (10%). To date, there has been no report which described any oncocytic change in bone and testicular tissues. In parallel with the literature, we observed no oncocytic transformation in the sections of the bone and testicular tissues from the NMO-treated rats.

Our study has both a limitation and strength. The limitation was the lack of histopathological evaluation of those three rats' organs. Even though those three deaths were unexpected during the experiment, the histopathological evaluation could not be performed, because the rats were found dead during daily observation, but not at the time of death; thus, the organs were not suitable for any examination. A future experiment with a live monitoring which gives an online signal to the investigators in case of any abnormality in vital signs of the rats would give a more accurate data about the deceased rats during the study. The strength of our study is the absence of any confounding factors which might influence the observed oncocytic transformation. All rats were kept in the same standard laboratory environment and killed within the same daytime period in 2 consecutive days to eliminate the circadian rhythm differences between the groups at the time of sacrifice.

In conclusion, we showed that NMO induced an oncocytic change in pancreas, thyroid, pituitary, and adrenal glands. To the best of our knowledge, no identified specific environmental risk factors that lead to an oncocytic transformation in endocrine glands have been reported previously. One reason for the lack of extensive research in this area may be that oncocytic lesions are often characterized as benign tumors, which may not be a priority for researchers. However, a few oncocytic malignant tumors such as oncocytic adrenocortical carcinoma, oncocytic intraductal carcinoma of pancreas, oncocytic differentiated, poorly differentiated and medullary thyroid carcinomas, have also been reported. Therefore, given the increasing prevalence of endocrine-disrupting chemicals in the environment, personal care products, manufactured goods and food sources, there is a need to advance our understanding of the pathological mechanisms underlying oncocytosis in endocrine organs.

**Author contributions**
All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by CÖ, TŞ, BYB, and GD. The first draft of the manuscript was written by EG, MS, and DK and all authors commented on previous versions of the manuscript. BÇ, ZC, and AS critically revised, edited the article and served as scientific advisors. All authors read and approved the final manuscript.

**Funding**
This work was supported by Kocaeli University, 2560, the Department of Scientific Research Projects.

**Availability of data and materials**
The data that support the findings of this study are available from the corresponding author upon reasonable request.

## Declarations

**Ethics approval and consent to participate**
Ethical approval of this study was obtained from the Animal Experiments Local Ethics Committee of Kocaeli University (KOÜ HADYEK 2/2-2021, 25.02.2021). This study was complied with all national and local regulations as a minimum standard with regard to the care and use of animals within our establishments.

**Competing interests**
The authors have no relevant financial or non-financial interests to disclose.

Received: 17 June 2023 Accepted: 10 January 2024
Published online: 20 January 2024

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