





# frontiers

## Frontiers eBook Copyright Statement

The copyright in the text of individual articles in this eBook is the property of their respective authors or their respective institutions or funders. The copyright in graphics and images within each article may be subject to copyright of other parties. In both cases this is subject to a license granted to Frontiers.

The compilation of articles constituting this eBook is the property of Frontiers.

Each article within this eBook, and the eBook itself, are published under the most recent version of the Creative Commons CC-BY licence.

The version current at the date of publication of this eBook is CC-BY 4.0. If the CC-BY licence is updated, the licence granted by Frontiers is automatically updated to the new version.

When exercising any right under the CC-BY licence, Frontiers must be attributed as the original publisher of the article or eBook, as applicable.

Authors have the responsibility of ensuring that any graphics or other materials which are the property of others may be included in the CC-BY licence, but this should be checked before relying on the CC-BY licence to reproduce those materials. Any copyright notices relating to those materials must be complied with.

Copyright and source acknowledgement notices may not be removed and must be displayed in any copy, derivative work or partial copy which includes the elements in question.

All copyright, and all rights therein, are protected by national and international copyright laws. The above represents a summary only. For further information please read Frontiers' Conditions for Website Use and Copyright Statement, and the applicable CC-BY licence.

ISSN 1664-8714

ISBN 978-2-88974-101-4

DOI 10.3389/978-2-88974-101-4

## About Frontiers

Frontiers is more than just an open-access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

## Frontiers Journal Series

The Frontiers Journal Series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the Frontiers Journal Series operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

## Dedication to Quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews. Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

## What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the Frontiers Journals Series: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area! Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers Editorial Office: [frontiersin.org/about/contact](https://frontiersin.org/about/contact)

## CORONAVIRUS DISEASE (COVID-19): PATHOPHYSIOLOGY, EPIDEMIOLOGY, CLINICAL MANAGEMENT AND PUBLIC HEALTH RESPONSE

Topic Editors:

**Zisis Kozlakidis**, International Agency For Research On Cancer (IARC), France

**Denise L. Doolan**, James Cook University, Australia

**Shen-Ying Zhang**, The Rockefeller University, United States

**Yasuko Tsunetsugu Yokota**, Tokyo University of Technology, Japan

**Tatsuo Shioda**, Osaka University, Japan

**Rukhsana Ahmed**, University at Albany, United States

**Mohan Jyoti Dutta**, Massey University, New Zealand

**Ata Murat Kaynar**, University of Pittsburgh, United States

**Michael Kogut**, Agricultural Research Service, United States Department of Agriculture, United States

**Hannah Bradby**, Uppsala University, Sweden

**Slobodan Paessler**, University of Texas Medical Branch at Galveston, United States

**Alex Rodriguez-Palacios**, Case Western Reserve University, United States

**Alexis M. Kalergis**, Pontificia Universidad Católica de Chile, Chile

**Longxiang Su**, Peking Union Medical College Hospital (CAMS), China

**Abdallah Samy**, University of Kansas, United States

**Zhongheng Zhang**, Sir Run Run Shaw Hospital, China

**Citation:** Kozlakidis, Z., Doolan, D. L., Zhang, S.-Y., Yokota, Y. T., Shioda, T., Ahmed, R., Dutta, M. J., Kaynar, A. M., Kogut, M., Bradby, H., Paessler, S., Rodriguez-Palacios, A., Kalergis, A. M., Su, L., Samy, A., Zhang, Z., eds. (2023). Coronavirus Disease (COVID-19): Pathophysiology, Epidemiology, Clinical Management and Public Health Response. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-88974-101-4

# Table of Contents

- 21 Editorial: Coronavirus Disease (COVID-19): Pathophysiology, Epidemiology, Clinical Management and Public Health Response**  
Denise L. Doolan, Zisis Kozlakidis, Zhongheng Zhang, Slobodan Paessler, Longxiang Su, Yasuko Tsunetsugu Yokota, Tatsuo Shioda, Alexander Rodriguez-Palacios, Ata Murat Kaynar, Rukhsana Ahmed, Abdallah Samy, Hannah Bradby, Alexis M. Kalergis, Mohan Jyoti Dutta, Michael Kogut and Shen-Ying Zhang
- 23 Forecasting COVID-19**  
Matjaž Perc, Nina Gorišek Miksić, Mitja Slavinec and Andraž Stožer
- 28 Coronavirus Disease (COVID-19) in Italy: Analysis of Risk Factors and Proposed Remedial Measures**  
Giuseppe Di Lorenzo and Rossella Di Trolio
- 32 Long-Term Neurological Threats of COVID-19: A Call to Update the Thinking About the Outcomes of the Coronavirus Pandemic**  
Antonio Pereira
- 35 COVID-19 and the Elderly: Who Cares?**  
Florian Fischer, Lea Raiber, Claudia Boscher and Maik H.-J. Winter
- 38 Coronavirus Pandemic (SARS-CoV-2): Pre-Exercise Screening Questionnaire (PESQ) for Telepresential Exercise**  
Leônidas de Oliveira Neto, Vagner Deuel de Oliveira Tavares, Felipe Barreto Schuch and Kenio Costa Lima
- 42 Is Pakistan's Response to Coronavirus (SARS-CoV-2) Adequate to Prevent an Outbreak?**  
Bilal Javed, Abdullah Sarwer, Erik B. Soto and Zia-ur-Rehman Mashwani
- 46 Renormalization Group Approach to Pandemics: The COVID-19 Case**  
Michele Della Morte, Domenico Orlando and Francesco Sannino
- 55 COVID-19 Infection and Circulating ACE2 Levels: Protective Role in Women and Children**  
Elena Ciaglia, Carmine Vecchione and Annibale Alessandro Puca
- 58 The Malnutritional Status of the Host as a Virulence Factor for New Coronavirus SARS-CoV-2**  
Matteo Briguglio, Fabrizio Ernesto Pregliasco, Giovanni Lombardi, Paolo Perazzo and Giuseppe Banfi
- 63 The Perfect Storm: Coronavirus (Covid-19) Pandemic Meets Overfat Pandemic**  
Philip B. Maffetone and Paul B. Laursen
- 69 SARS-CoV-2 and the Use of Chloroquine as an Antiviral Treatment**  
Mathieu E. Rebeaud and Florian Zores
- 74 Does COVID-19 Spread Through Droplets Alone?**  
Thushara Galbadage, Brent M. Peterson and Richard S. Gunasekera
- 78 The Role of Hydroxychloroquine in Coronavirus Disease 2019. A Versatile Tool at the Service of Humanity**  
Argyris Tzouvelekis, Theodoros Karampitsakos and Demosthenes Bouros

- 80** *Serological Approaches for COVID-19: Epidemiologic Perspective on Surveillance and Control*  
Cheryl Yi-Pin Lee, Raymond T. P. Lin, Laurent Renia and Lisa F. P. Ng
- 87** *Use of Corticosteroids in Coronavirus Disease 2019 Pneumonia: A Systematic Review of the Literature*  
Nicola Veronese, Jacopo Demurtas, Lin Yang, Roberto Tonelli, Mario Barbagallo, Pierluigi Lopalco, Erik Lagolio, Stefano Celotto, Damiano Pizzol, Liye Zou, Mark A. Tully, Petre Cristian Ilie, Mike Trott, Guillermo F. López-Sánchez and Lee Smith
- 93** *Role of the Eye in Transmitting Human Coronavirus: What We Know and What We Do Not Know*  
Chuan-bin Sun, Yue-ye Wang, Geng-hao Liu and Zhe Liu
- 100** *COVID-19 Trend Estimation in the Elderly Italian Region of Sardinia*  
Mariangela Valentina Puci, Federica Loi, Ottavia Eleonora Ferraro, Stefano Cappai, Sandro Rolesu and Cristina Montomoli
- 110** *Gender Differences in Patients With COVID-19: Focus on Severity and Mortality*  
Jian-Min Jin, Peng Bai, Wei He, Fei Wu, Xiao-Fang Liu, De-Min Han, Shi Liu and Jin-Kui Yang
- 116** *Coronavirus Disease-2019: Knowledge, Attitude, and Practices of Health Care Workers at Makerere University Teaching Hospitals, Uganda*  
Ronald Olum, Gaudencia Chekwech, Godfrey Wekha, Dianah Rhoda Nassozi and Felix Bongomin
- 125** *Hydroxychloroquine: A Familiar Agent to Combat the Pandemic of COVID-19*  
Vasilios M. Polymeropoulos
- 127** *Chaos, Percolation and the Coronavirus Spread*  
Aldo Bonasera and Suyalatu Zhang
- 132** *Could the Inhibition of Endo-Lysosomal Two-Pore Channels (TPCs) by the Natural Flavonoid Naringenin Represent an Option to Fight SARS-CoV-2 Infection?*  
Antonio Filippini, Antonella D'Amore, Fioretta Palombi and Armando Carpaneto
- 136** *Potential SARS-CoV-2 Preimmune IgM Epitopes*  
Velizar Shivarov, Peter K. Petrov and Anastas D. Pashov
- 141** *Age-Dependent Risks of Incidence and Mortality of COVID-19 in Hubei Province and Other Parts of China*  
Hongdou Li, Shuang Wang, Fan Zhong, Wuyin Bao, Yipeng Li, Lei Liu, Hongyan Wang and Yungang He
- 147** *COVID-19: Cultural Predictors of Gender Differences in Global Prevalence Patterns*  
Olav T. Muurlink and Andrew W. Taylor-Robinson
- 149** *Covid-19: A Dynamic Analysis of Fatality Risk in Italy*  
Marco Iosa, Stefano Paolucci and Giovanni Morone
- 154** *COVID-19 and Bangladesh: Challenges and How to Address Them*  
Saeed Anwar, Mohammad Nasrullah and Mohammad Jakir Hosen

- 162** *Novel Coronavirus Disease 2019 Infection in Children: The Dark Side of a Worldwide Outbreak*  
Danilo Buonsenso, Giuseppe Zampino and Piero Valentini
- 165** *Are Children Most of the Submerged Part of SARS-CoV-2 Iceberg?*  
Stefano Passanisi, Fortunato Lombardo, Giuseppina Salzano and Giovanni Battista Pajno
- 168** *High Resolution CT Imaging Dynamic Follow-Up Study of Novel Coronavirus Pneumonia*  
Xuefang Lu, Wei Gong, Zhoufeng Peng, Feifei Zeng and Fang Liu
- 175** *Diabetic Kidney Disease and COVID-19: The Crash of Two Pandemics*  
Luis D'Marco, Maria Jesús Puchades, Maria Romero-Parra and Jose Luis Gorriz
- 178** *Coronavirus Disease 2019 Emergency and Cancer in the South of Italy: What's New for the Oncologist?*  
Concetta Ingenito, Luciana Buonerba, Claudia Ferrara, Giuseppina Busto, Annamaria Libroia, Gianluca Ragone, Emilio Leo, Beatrice Savastano, Concetta Dello Iorio, Ferdinando De Falco, Simona Iaccarino, Luciano Tarantino, Mario Polverino and Giuseppe Di Lorenzo
- 181** *Extended SIR Prediction of the Epidemics Trend of COVID-19 in Italy and Compared With Hunan, China*  
Jia Wangping, Han Ke, Song Yang, Cao Wenzhe, Wang Shengshu, Yang Shanshan, Wang Jianwei, Kou Fuyin, Tai Penggang, Li Jing, Liu Miao and He Yao
- 188** *The Battle Against COVID-19 in Jordan: An Early Overview of the Jordanian Experience*  
Ala'a B. Al-Tammemi
- 194** *Evaluation of the Secondary Transmission Pattern and Epidemic Prediction of COVID-19 in the Four Metropolitan Areas of China*  
Longxiang Su, Na Hong, Xiang Zhou, Jie He, Yingying Ma, Huizhen Jiang, Lin Han, Fengxiang Chang, Guangliang Shan, Weiguo Zhu and Yun Long
- 203** *Development and Potential Usefulness of the COVID-19 Ag Respi-Strip Diagnostic Assay in a Pandemic Context*  
Pascal Mertens, Nathalie De Vos, Delphine Martiny, Christian Jassoy, Ali Mirazimi, Lize Cuypers, Sigi Van den Wijngaert, Vanessa Monteil, Pierrette Melin, Karolien Stoffels, Nicolas Yin, Davide Mileto, Sabrina Delaunoy, Henri Magein, Katrien Lagrou, Justine Bouzet, Gabriela Serrano, Magali Wautier, Thierry Leclipteux, Marc Van Ranst, Olivier Vandenberg and LHUB-ULB SARS-CoV-2 working diagnostic group
- 214** *Comparison of Epidemiological Variations in COVID-19 Patients Inside and Outside of China—A Meta-Analysis*  
Ali Ahmed, Areeba Ali and Sana Hasan
- 224** *Confinement Time Required to Avoid a Quick Rebound of COVID-19: Predictions From a Monte Carlo Stochastic Model*  
Társilo Girona
- 231** *Clinical Time Features and Chest Imaging of 85 Patients With COVID-19 in Zhuhai, China*  
Zhuobing Liu, Li Ding, Gongqi Chen, Chaohui Zhao, Xiaoqing Luo, Xinghua Li, Wentao Luo, Jinyu Xia and Xi Liu

- 241** *Using Probiotics to Flatten the Curve of Coronavirus Disease COVID-2019 Pandemic*  
David Baud, Varvara Dimopoulou Agri, Glenn R. Gibson, Gregor Reid and Eric Giannoni
- 246** *Could BCG Vaccination Induce Protective Trained Immunity for SARS-CoV-2?*  
Camila Covián, Angello Retamal-Díaz, Susan M. Bueno and Alexis M. Kalergis
- 253** *Doxycycline: From Ocular Rosacea to COVID-19 Anosmia. New Insight Into the Coronavirus Outbreak*  
Chiara Bonzano, Davide Borroni, Andrea Lancia and Elisabetta Bonzano
- 257** *Pangolins Lack IFIH1/MDA5, a Cytoplasmic RNA Sensor That Initiates Innate Immune Defense Upon Coronavirus Infection*  
Heinz Fischer, Erwin Tschachler and Leopold Eckhart
- 263** *How the Italian NHS Is Fighting Against the COVID-19 Emergency*  
Stefania Boccia, Fidelia Cascini, Martin McKee and Walter Ricciardi
- 266** *COVID-19: The Conjunction of Events Leading to the Coronavirus Pandemic and Lessons to Learn for Future Threats*  
Roger Frutos, Marc Lopez Roig, Jordi Serra-Cobo and Christian A. Devaux
- 271** *Implications of COVID-19 Outbreak on Immune Therapies in Multiple Sclerosis Patients—Lessons Learned From SARS and MERS*  
Nora Möhn, Refik Pul, Christoph Kleinschnitz, Harald Prüss, Torsten Witte, Martin Stangel and Thomas Skripuletz
- 276** *Recommendations for Physical Inactivity and Sedentary Behavior During the Coronavirus Disease (COVID-19) Pandemic*  
Fabrizio Ricci, Pascal Izzicupo, Federica Moscucci, Susanna Sciomer, Silvia Maffei, Angela Di Baldassarre, Anna Vittoria Mattioli and Sabina Gallina
- 280** *HIV and SARS-Coronavirus-2 Epidemics: Possible Interactions and Need for Studies, Especially in Africa*  
Francesca Cainelli, Bartholomew Dzudzor, Massimiliano Lanzafame, Adonis Goushchi, Sirika Chhem and Sandro Vento
- 284** *Highlight of Immune Pathogenic Response and Hematopathologic Effect in SARS-CoV, MERS-CoV, and SARS-Cov-2 Infection*  
Yanwen Liang, Mong-Lien Wang, Chian-Shiu Chien, Aliaksandr A. Yarmishyn, Yi-Ping Yang, Wei-Yi Lai, Yung-Hung Luo, Yi-Tsung Lin, Yann-Jang Chen, Pei-Ching Chang and Shih-Hwa Chiou
- 295** *Clinical Characteristics and Reasons for Differences in Duration From Symptom Onset to Release From Quarantine Among Patients With COVID-19 in Liaocheng, China*  
Suo Chen Tian, Zhenqin Chang, Yunxia Wang, Min Wu, Wenming Zhang, Guijie Zhou, Xiuli Zou, Hui Tian, Tingfang Xiao, Junmin Xing, Juan Chen, Jian Han, Kang Ning and Tiejun Wu
- 303** *Coronavirus and Obesity: Could Insulin Resistance Mediate the Severity of Covid-19 Infection?*  
Francis M. Finucane and Colin Davenport
- 308** *Commentary: Coronavirus and Obesity: Could Insulin Resistance Mediate the Severity of Covid-19 Infection?*  
Vincenza Frisardi

- 311** *The Novel Coronavirus COVID-19 Outbreak: Global Implications for Antimicrobial Resistance*  
Aimee K. Murray
- 315** *Severe COVID-19: A Review of Recent Progress With a Look Toward the Future*  
Peng Xie, Wanyu Ma, Hongbo Tang and Daishun Liu
- 322** *Developments, Evolution, and Implications of National Diagnostic Criteria for COVID-19 in China*  
Lin-Lu Ma, Bui-Hui Li, Ying-Hui Jin, Tong Deng, Xue-Qun Ren and Xian-Tao Zeng
- 328** *May Polyphenols Have a Role Against Coronavirus Infection? An Overview of in vitro Evidence*  
Giuseppe Annunziata, Marco Sanduzzi Zamparelli, Ciro Santoro, Roberto Ciampaglia, Mariano Stornaiuolo, Gian Carlo Tenore, Alessandro Sanduzzi and Ettore Novellino
- 335** *Comparative Analysis of Early-Stage Clinical Features Between COVID-19 and Influenza A H1N1 Virus Pneumonia*  
Changxing Shen, Min Tan, Xiaolian Song, Guoliang Zhang, Jiren Liang, Hong Yu and Changhui Wang
- 342** *On Determining the Age Distribution of COVID-19 Pandemic*  
Dominic Cortis
- 345** *Clinical Features, Diagnosis, and Treatment of COVID-19 in Hospitalized Patients: A Systematic Review of Case Reports and Case Series*  
Azin Tahvildari, Mahta Arbabi, Yeganeh Farsi, Parnian Jamshidi, Saba Hasanzadeh, Tess Moore Calcagno, Mohammad Javad Nasiri and Mehdi Mirsaedi
- 355** *Therapeutic Algorithm for Use of Melatonin in Patients With COVID-19*  
Russel J. Reiter, Pedro Abreu-Gonzalez, Paul E. Marik and Alberto Dominguez-Rodriguez
- 362** *Interferon- $\alpha$ 2b Treatment for COVID-19*  
Qiong Zhou, Virginia Chen, Casey P. Shannon, Xiao-Shan Wei, Xuan Xiang, Xu Wang, Zi-Hao Wang, Scott J. Tebbutt, Tobias R. Kollmann and Eleanor N. Fish
- 368** *Corrigendum: Interferon- $\alpha$ 2b Treatment for COVID-19*  
Qiong Zhou, Virginia Chen, Casey P. Shannon, Xiao-Shan Wei, Xuan Xiang, Xu Wang, Zi-Hao Wang, Scott J. Tebbutt, Tobias R. Kollmann and Eleanor N. Fish
- 370** *Is SARS-CoV-2 Vertically Transmitted?*  
Ana Cristina Simões e Silva and Caio Ribeiro Vieira Leal
- 375** *Humoral Immune Responses in COVID-19 Patients: A Window on the State of the Art*  
Gabriel Siracusano, Claudia Pastori and Lucia Lopalco
- 384** *Therapeutic Options for Coronavirus Disease 2019 (COVID-19) - Modulation of Type I Interferon Response as a Promising Strategy?*  
Aurélien Mary, Lucie Hénaut, Jean-Luc Schmit, Jean-Philippe Lanoix and Michel Brazier



- 388** *In Search of Wise Management of Medical Resources and Personnel in the Long Combat With Coronavirus*  
Yi-ru Hu, Mingqia Wang and Bin Zhang
- 391** *Coronavirus Disease (COVID-19) in the Middle East: A Call for a Unified Response*  
Tania Sawaya, Tala Ballouz, Hassan Zaraket and Nesrine Rizk
- 394** *Three Novel COVID-19 Pneumonia Cases Successfully Treated With Lopinavir/Ritonavir*  
Tatsuhiko Wada, Kosuke Shimode, Takayuki Hoshiyama, Yoko Takayama and Kunihiro Yamaoka
- 399** *Official Data and Analytical Forecasts: Differences and Similarities Among Coronavirus Disease (COVID-19) Confirmed Cases and Deaths*  
Ottavia Eleonora Ferraro, Mariangela Valentina Puci, Cristina Montomoli, Sandro Rolesu, Stefano Cappai and Federica Loi
- 404** *MSC Therapies for COVID-19: Importance of Patient Coagulopathy, Thromboprophylaxis, Cell Product Quality and Mode of Delivery for Treatment Safety and Efficacy*  
Guido Moll, Norman Drzeniek, Julian Kamhieh-Milz, Sven Geissler, Hans-Dieter Volk and Petra Reinke
- 414** *COVID19: A Systematic Approach to Early Identification and Healthcare Worker Protection*  
Yu Zhao, Chong Cui, Kun Zhang, Jialin Liu, Jinfu Xu, Eric Nisenbaum, Yixiang Huang, Guoyou Qin, Bing Chen, Michael Hoffer, Susan H. Blanton, Fred Telischi, Joshua M. Hare, Sylvia Daunert, Bhavarth Shukla, Savita G. Pahwa, Dushyantha T. Jayaweera, Paul E. Farmer, Carlos del Rio, Xuezhong Liu and Yilai Shu
- 422** *Novel Coronavirus-Induced NLRP3 Inflammasome Activation: A Potential Drug Target in the Treatment of COVID-19*  
Adnan Shah
- 427** *Epidemiologic Characteristics, Transmission Chain, and Risk Factors of Severe Infection of COVID-19 in Tianjin, a Representative Municipality City of China*  
Jin Wang, Zhihui Li, Xiaomin Cheng, Huan Hu, Conghui Liao, Pengyuan Li, Jiahai Lu and Zeliang Chen
- 436** *Approaches to Daily Monitoring of the SARS-CoV-2 Outbreak in Northern Italy*  
Giovenale Moirano, Lorenzo Richiardi, Carlo Novara and Milena Maule
- 443** *Epidemiological and Clinical Characteristics of Patients With Coronavirus Disease-2019 in Shiyan City, China*  
Long Liu, Xu Lei, Xiao Xiao, Jing Yang, Jian Li, Manshan Ji, Weixing Du, Huabing Tan, Jianyong Zhu, Bei Li, Zhixiong Jin, Weiyong Liu, Jianguo Wu and Zhixin Liu
- 452** *Lung Surfactant for Pulmonary Barrier Restoration in Patients With COVID-19 Pneumonia*  
Ursula Mirastschijski, Rolf Dembinski and Kathrin Maedler
- 456** *Forecasting and Evaluating Multiple Interventions for COVID-19 Worldwide*  
Zixin Hu, Qiyang Ge, Shudi Li, Eric Boerwinkle, Li Jin and Momiao Xiong

- 467** *The Rise and Impact of COVID-19 in India*  
S. Udhaya Kumar, D. Thirumal Kumar, B. Prabhu Christopher and C. George Priya Doss
- 474** *The Lung, the Heart, the Novel Coronavirus, and the Renin-Angiotensin System; The Need for Clinical Trials*  
Eugenie R. Lumbers, Sarah J. Delforce, Kirsty G. Pringle and Gary R. Smith
- 481** *Growth Rate and Acceleration Analysis of the COVID-19 Pandemic Reveals the Effect of Public Health Measures in Real Time*  
Yuri Tani Utsunomiya, Adam Taiti Harth Utsunomiya, Rafaela Beatriz Pintor Torrecilha, Silvana de Cássia Paulan, Marco Milanese and José Fernando Garcia
- 490** *SARS-CoV-2 Infection and the Newborn*  
Fahri Ovali
- 501** *Novel Insights Into Illness Progression and Risk Profiles for Mortality in Non-survivors of COVID-19*  
Liang Shao, Xinyi Li, Yi Zhou, Yalan Yu, Yanan Liu, Minghui Liu, Ruixian Zhang, Haojian Zhang, Xinghuan Wang and Fuling Zhou
- 511** *New Insights of Emerging SARS-CoV-2: Epidemiology, Etiology, Clinical Features, Clinical Treatment, and Prevention*  
Gangqiang Guo, Lele Ye, Kan Pan, Yu Chen, Dong Xing, Kejing Yan, Zhiyuan Chen, Ning Ding, Wenshu Li, Hong Huang, Lifang Zhang, Xiaokun Li and Xiangyang Xue
- 533** *Methylation Pathways and SARS-CoV-2 Lung Infiltration and Cell Membrane-Virus Fusion Are Both Subject to Epigenetics*  
Leo Pruumboom
- 538** *Do Humidity and Temperature Impact the Spread of the Novel Coronavirus?*  
Shu Yuan, Si-Cong Jiang and Zi-Lin Li
- 542** *The Role of Transthoracic Ultrasound in the novel Coronavirus Disease (COVID-19): A Reappraisal. Information and Disinformation: Is There Still Place for a Scientific Debate?*  
Carla Maria Irene Quarato, Mariapia Venuti, Donato Lacedonia, Anna Simeone, Lucia Maria Cecilia Dimitri, Gaetano Rea, Beatrice Ferragalli and Marco Sperandeo
- 547** *The Lessons and Experiences That Can Be Learned From China in Fighting Coronavirus Disease 2019*  
Jianli Liu, Guangming Zhang, Feng Zhang and Chunjuan Song
- 551** *Could SARS-CoV-2-Induced Hyperinflammation Magnify the Severity of Coronavirus Disease (CoViD-19) Leading to Acute Respiratory Distress Syndrome?*  
A. S. Smiline Girija, Esaki M. Shankar and Marie Larsson
- 556** *Fighting the Host Reaction to SARS-COV-2 in Critically Ill Patients: The Possible Contribution of Off-Label Drugs*  
Stefania Scala and Roberto Pacelli
- 562** *Textile Masks and Surface Covers—A Spray Simulation Method and a “Universal Droplet Reduction Model” Against Respiratory Pandemics*  
Alex Rodriguez-Palacios, Fabio Cominelli, Abigail R. Basson, Theresa T. Pizarro and Sanja Ilic

- 573** *Guideline-Based Chinese Herbal Medicine Treatment Plus Standard Care for Severe Coronavirus Disease 2019 (G-CHAMPS): Evidence From China*  
Yong-an Ye and The G-CHAMPS Collaborative Group
- 579** *Psycho-Neuroendocrine-Immune Interactions in COVID-19: Potential Impacts on Mental Health*  
Ícaro Raony, Camila Saggiore de Figueiredo, Pablo Pandolfo, Elizabeth Giestal-de-Araujo, Priscilla Oliveira-Silva Bomfim and Wilson Savino
- 594** *Knowledge, Attitude and Practice Toward COVID-19 Among the Public in the Kingdom of Saudi Arabia: A Cross-Sectional Study*  
Mohammed K. Al-Hanawi, Khadijah Angawi, Noor Alshareef, Ameerah M. N. Qattan, Hoda Z. Helmy, Yasmin Abudawood, Mohammed Alqurashi, Waleed M. Kattan, Nasser Akeil Kadasah, Gowokani Chijere Chirwa and Omar Alsharqi
- 604** *Thalidomide-Revisited: Are COVID-19 Patients Going to Be the Latest Victims of Yet Another Theoretical Drug-Repurposing?*  
Athar Khalil, Amina Kamar and Georges Nemer
- 611** *Symptomatic Protective Action of Glycyrrhizin (Licorice) in COVID-19 Infection?*  
Harald Murck
- 616** *Vitamin D Deficiency and Air Pollution Exacerbate COVID-19 Through Suppression of Antiviral Peptide LL37*  
Mardi A. Crane-Godreau, Kathleen J. Clem, Peter Payne and Steven Fiering
- 621** *Innate Immune Signaling and Proteolytic Pathways in the Resolution or Exacerbation of SARS-CoV-2 in Covid-19: Key Therapeutic Targets?*  
Jean-Michel Sallenave and Loïc Guillot
- 630** *A Simulation of a COVID-19 Epidemic Based on a Deterministic SEIR Model*  
José M. Carcione, Juan E. Santos, Claudio Bagaini and Jing Ba
- 643** *The Biology of Lactoferrin, an Iron-Binding Protein That Can Help Defend Against Viruses and Bacteria*  
Douglas B. Kell, Eugene L. Heyden and Etheresia Pretorius
- 658** *Coronavirus Disease (Covid-19): What Are We Learning in a Country With High Mortality Rate?*  
Luciano Mutti, Francesca Pentimalli, Giovanni Baglio, Patrizia Maiorano, Rita Emilena Saladino, Pierpaolo Correale and Antonio Giordano
- 663** *COVID-19: Emergence, Spread, Possible Treatments, and Global Burden*  
Raghuvir Keni, Anila Alexander, Pawan Ganesh Nayak, Jayesh Mudgal and Krishnadas Nandakumar
- 676** *Case Report: Clinical Treatment of the First Critical Patient With Coronavirus Disease (COVID-19) in Liaocheng, Shandong Province*  
Hui Tian, Yuanda Sui, Suochen Tian, Xiuli Zou, Zhiping Xu, Huang He and Tiejun Wu
- 683** *Knowledge and Information Sources About COVID-19 Among University Students in Jordan: A Cross-Sectional Study*  
Amin N. Olaimat, Iman Aolymat, Hafiz M. Shahbaz and Richard A. Holley

- 692 *Medical Students and COVID-19: Knowledge, Attitudes, and Precautionary Measures. A Descriptive Study From Jordan***  
Ashraf I. Khasawneh, Anas Abu Humeidan, Jomana W. Alsulaiman, Sarah Bloukh, Mohannad Ramadan, Tariq N. Al-Shatanawi, Hasan H. Awad, Waleed Y. Hijazi, Kinda R. Al-Kammash, Nail Obeidat, Tareq Saleh and Khalid A. Kheirallah
- 701 *Predicting COVID-19 Peaks Around the World***  
Constantino Tsallis and Ugur Tirnakli
- 707 *Clinical Implications of Chloroquine and Hydroxychloroquine Ototoxicity for COVID-19 Treatment: A Mini-Review***  
Pattarawadee Prayuenyong, Anand V. Kasbekar and David M. Baguley
- 713 *Status and Challenges of Public Health Emergency Management in China Related to COVID-19***  
Yulong Cao, Jiao Shan, Zhizhong Gong, Jiqiu Kuang and Yan Gao
- 719 *Effectiveness of Arbidol for COVID-19 Prevention in Health Professionals***  
Chunguang Yang, Chunjin Ke, Daoyuan Yue, Wengang Li, Zhiquan Hu, Wei Liu, Shuhua Hu, Shaogang Wang and Jihong Liu
- 725 *Clinical and Epidemiological Characteristics of COVID-19 Patients in Chongqing China***  
Ao Yang, Qian Qiu, Xianghua Kong, Yanyu Sun, Tingying Chen, Yujie Zuo, Danfeng Yuan, Wei Dai, Jihong Zhou and Anzhou Peng
- 733 *An Online Observational Study of Patients With Olfactory and Gustatory Alterations Secondary to SARS-CoV-2 Infection***  
Patricia Gómez-Iglesias, Jesús Porta-Etessam, Teresa Montalvo, Adrián Valls-Carbó, Vicente Gajate, Jordi A. Matías-Guiu, Beatriz Parejo-Carbonell, Nuria González-García, David Ezpeleta, José Miguel Láinez and Jorge Matías-Guiu
- 738 *Transmission of SARS-CoV-2 and Other Infections at Large Sports Gatherings: A Surprising Gap in Our Knowledge***  
Michele Sassano, Martin McKee, Walter Ricciardi and Stefania Boccia
- 741 *Epidemiological Trends of Coronavirus Disease 2019 in China***  
Bilin Chen, Huanhuan Zhong, Yueyan Ni, Lulu Liu, Jinjin Zhong and Xin Su
- 749 *COVID-19 and SARS Coronavirus 2: Antibodies for the Immediate Rescue and Recovery Phase***  
Scott B. Halstead and Ramesh Akkina
- 751 *Lessons Learned to Date on COVID-19 Hyperinflammatory Syndrome: Considerations for Interventions to Mitigate SARS-CoV-2 Viral Infection and Detrimental Hyperinflammation***  
Marco Cardone, Masahide Yano, Amy S. Rosenberg and Montserrat Puig
- 760 *Challenges in Abdominal Organ Transplantation During the COVID-19 Pandemic***  
Stepan M. Esagian, Ioannis A. Ziogas, Dimitrios Giannis, Muhammad H. Hayat, Nahel Elias and Georgios Tsoulfas
- 768 *Laboratory Testing Methods for Novel Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2)***  
Roshan J. D'Cruz, Arthur W. Currier and Valerie B. Sampson

- 779** *Activity and Health During the SARS-CoV2 Pandemic (ASAP): Study Protocol for a Multi-National Network Trial*  
Jan Wilke, Lisa Mohr, Adam S. Tenforde, Oliver Vogel, Luiz Hespanhol, Lutz Vogt, Evert Verhagen and Karsten Hollander
- 786** *Coronavirus Disease Pandemic Is a Real Challenge for Brazil*  
Ana Cristina Simões e Silva, Eduardo A. Oliveira and Hercilio Martelli Jr.
- 789** *A Novel Scoring System for Prediction of Disease Severity in COVID-19*  
Chi Zhang, Ling Qin, Kang Li, Qi Wang, Yan Zhao, Bin Xu, Lianchun Liang, Yanchao Dai, Yingmei Feng, Jianping Sun, Xuemei Li, Zhongjie Hu, Haiping Xiang, Tao Dong, Ronghua Jin and Yonghong Zhang
- 796** *The Lung Macrophage in SARS-CoV-2 Infection: A Friend or a Foe?*  
Zaid Abassi, Yara Knaney, Tony Karram and Samuel N. Heyman
- 801** *ACE2, Much More Than Just a Receptor for SARS-COV-2*  
Lobelia Samavati and Bruce D. Uhal
- 810** *Identification of RT-PCR-Negative Asymptomatic COVID-19 Patients via Serological Testing*  
Jinru Wu, Xinyi Liu, Dan Zhou, Guangqian Qiu, Miao Dai, Qingting Yang, Zhonghui Pan, Ning Zhou and Pa Wu
- 815** *The Status of Psychological Issues Among Frontline Health Workers Confronting the Coronavirus Disease 2019 Pandemic*  
Zeming Hu and Bin Chen
- 818** *Are They Just Two Children COVID-19 Cases Confused With Flu?*  
Biao Zou, Di Ma, Yinhu Li, Liru Qiu, Yu Chen, Yan Hao, Xiaoping Luo and Sainan Shu
- 823** *SARS-CoV-2 Genome Analysis of Japanese Travelers in Nile River Cruise*  
Tsuyoshi Sekizuka, Sanae Kuramoto, Eri Nariai, Masakatsu Taira, Yushi Hachisu, Akihiko Tokaji, Michiyo Shinohara, Tsuyoshi Kishimoto, Kentaro Itokawa, Yusuke Kobayashi, Keisuke Kadokura, Hajime Kamiya, Tamano Matsui, Motoi Suzuki and Makoto Kuroda
- 829** *The Clinical Characteristics and Prognosis Factors of Mild-Moderate Patients With COVID-19 in a Mobile Cabin Hospital: A Retrospective, Single-Center Study*  
Jishou Zhang, Menglong Wang, Mengmeng Zhao, Shanshan Guo, Yao Xu, Jing Ye, Wen Ding, Zhen Wang, Di Ye, Wei Pan, Menglin Liu, Dan Li, Zhen Luo, Jianfang Liu and Jun Wan
- 840** *Main Clinical Features of COVID-19 and Potential Prognostic and Therapeutic Value of the Microbiota in SARS-CoV-2 Infections*  
Yu He, Jianhui Wang, Fang Li and Yuan Shi
- 847** *Could Coronavirus Disease 2019 (COVID-19) Render Natural Immunity to Re-infections? A Spotlight on the Therapeutic Pipeline*  
Muhammad Abbas Abid, Loren Nunley and Muhammad Bilal Abid
- 850** *A Retrospective Analysis of the Clinical and Epidemiological Characteristics of COVID-19 Patients in Henan Provincial People's Hospital, Zhengzhou, China*  
Jing Zhao, Hao-Yu Gao, Zi-Yi Feng and Qi-Jun Wu
- 860** *Impact of Lockdown on the Epidemic Dynamics of COVID-19 in France*  
Lionel Roques, Etienne K. Klein, Julien Papaïx, Antoine Sar and Samuel Soubeyrand

- 867** *Antibody Dependent Enhancement Due to Original Antigenic Sin and the Development of SARS*  
Walter Fierz and Brigitte Walz
- 872** *Transitioning Out of the Coronavirus Lockdown: A Framework for Evaluating Zone-Based Social Distancing*  
Eric Friedman, John Friedman, Simon Johnson and Adam Landsberg
- 877** *Hyperlocal Postcode Based Crowdsourced Surveillance Systems in the COVID-19 Pandemic Response*  
Ajay Hegde, Ramesh Masthi and Darshan Krishnappa
- 880** *Risk Factors Associated With Long-Term Hospitalization in Patients With COVID-19: A Single-Centered, Retrospective Study*  
Yiqun Wu, Bingbo Hou, Jielan Liu, Yingying Chen and Ping Zhong
- 890** *Could Sex/Gender Differences in ACE2 Expression in the Lungs Contribute to the Large Gender Disparity in the Morbidity and Mortality of Patients Infected With the SARS-CoV-2 Virus?*  
Gregor Majdic
- 893** *Early Detection and Assessment of Covid-19*  
Hafiz Abdul Sattar Hashmi and Hafiz Muhammad Asif
- 901** *Analysis of Possible Intermediate Hosts of the New Coronavirus SARS-CoV-2*  
Shu Yuan, Si-Cong Jiang and Zi-Lin Li
- 906** *Transmission of SARS-CoV-2, Required Developments in Research and Associated Public Health Concerns*  
Suliman Khan, Jianbo Liu and Mengzhou Xue
- 914** *Clinical Characteristics of COVID-19 Patients With Gastrointestinal Symptoms: An Analysis of Seven Patients in China*  
Jin-Wei Ai, Hao Zi, Yong Wang, Qiao Huang, Na Wang, Lu-Yao Li, Bin Pei, Jianguang Ji and Xian-Tao Zeng
- 923** *Cystic Fibrosis: Fighting Together Against Coronavirus Infection*  
Sara Manti, Giuseppe Fabio Parisi, Maria Papale, Enza Mulè, Donatella Aloisio, Novella Rotolo and Salvatore Leonardi
- 928** *Immune-Inflammatory Parameters in COVID-19 Cases: A Systematic Review and Meta-Analysis*  
Xudong Feng, Shuangshuang Li, Qiang Sun, Jiaqi Zhu, Bo Chen, Maoming Xiong and Guodong Cao
- 942** *Biosurfactants: A Covid-19 Perspective*  
Matthew L. Smith, Stefano Gandolfi, Philippa M. Coshall and Pattanathu K. S. M. Rahman
- 950** *Recent Understandings Toward Coronavirus Disease 2019 (COVID-19): From Bench to Bedside*  
Jie Yu, Peiwei Chai, Shengfang Ge and Xianqun Fan
- 962** *Interferon-Induced Transmembrane Protein (IFITM3) Is Upregulated Explicitly in SARS-CoV-2 Infected Lung Epithelial Cells*  
Mahmood Yaseen Hachim, Saba Al Heialy, Ibrahim Yaseen Hachim, Rabih Halwani, Abiola C. Senok, Azzam A. Maghazachi and Qutayba Hamid

- 971 *How and When to End the COVID-19 Lockdown: An Optimization Approach***  
Thomas Rawson, Tom Brewer, Dessislava Veltcheva, Chris Huntingford and Michael B. Bonsall
- 982 *Activation of TLR7 and Innate Immunity as an Efficient Method Against COVID-19 Pandemic: Imiquimod as a Potential Therapy***  
Konstantinos Poulas, Konstantinos Farsalinos and Charilaos Zanidis
- 984 *Epidemiological and Clinical Characteristics of Cases During the Early Phase of COVID-19 Pandemic: A Systematic Review and Meta-Analysis***  
Jiayun Koh, Shimoni Urvish Shah, Pearleen Ee Yong Chua, Hao Gui and Junxiong Pang
- 999 *SARS-CoV-2 Pathogenesis: Imbalance in the Renin-Angiotensin System Favors Lung Fibrosis***  
M. Victoria Delpino and Jorge Quarleri
- 1004 *Prejudice Toward Asian Americans in the Covid-19 Pandemic: The Effects of Social Media Use in the United States***  
Stephen M. Croucher, Thao Nguyen and Diyako Rahmani
- 1016 *Poverty and Covid-19: Rates of Incidence and Deaths in the United States During the First 10 Weeks of the Pandemic***  
W. Holmes Finch and Maria E. Hernández Finch
- 1026 *COVID-19: An Appeal for an Intersectoral Approach to Tackle With the Emergency***  
Alessandra Scagliarini and Alberto Alberti
- 1035 *COVID-19 Is Further Subdivided Into COVIP-19 and COVII-19***  
Shiliang Song
- 1037 *The COVID-19 Cytokine Storm; What We Know So Far***  
Dina Ragab, Haitham Salah Eldin, Mohamed Taeimah, Rasha Khattab and Ramy Salem
- 1041 *Potential Treatments for COVID-19 Related Cytokine Storm - Beyond Corticosteroids***  
Yi Miao, Lei Fan and Jian-Yong Li
- 1044 *Immune Response, Inflammation, and the Clinical Spectrum of COVID-19***  
Luis F. García
- 1057 *Ethical Criteria for the Admission and Management of Patients in the ICU Under Conditions of Limited Medical Resources: A Shared International Proposal in View of the COVID-19 Pandemic***  
Vittoradolfo Tambone, Donald Boudreau, Massimo Ciccozzi, Karen Sanders, Laura Leondina Campanozzi, Jane Wathuta, Luciano Violante, Roberto Cauda, Carlo Petrini, Antonio Abbate, Rossana Alloni, Josepmaria Argemi, Josep Argemí Renom, Anna De Benedictis, France Galerneau, Emilio García-Sánchez, Giampaolo Ghilardi, Janet Palmer Hafler, Magdalena Linden, Alfredo Marcos, Andrea Onetti Muda, Marco Pandolfi, Thierry Pelaccia, Mario Picozzi, Ruben Oscar Revello, Giovanna Ricci, Robert Rohrbaugh, Patrizio Rossi, Ascanio Sirignano, Antonio Gioacchino Spagnolo, Trevor Stammers, Lourdes Velázquez, Evandro Agazzi and Mark Mercurio

- 1060 Development and Validation of a Rapid, Single-Step Reverse Transcriptase Loop-Mediated Isothermal Amplification (RT-LAMP) System Potentially to Be Used for Reliable and High-Throughput Screening of COVID-19**  
Minghua Jiang, Weihua Pan, Amir Arasthfer, Wenjie Fang, Liyan Ling, Hua Fang, Farnaz Daneshnia, Jian Yu, Wanqing Liao, Hao Pei, Xiaojing Li and Cornelia Lass-Flörl
- 1066 COVID-19 Is Distinct From SARS-CoV-2-Negative Community-Acquired Pneumonia**  
Yutian Zhou, Shujin Guo, Ye He, Qiunan Zuo, Danju Liu, Meng Xiao, Jinxiu Fan and Xiaohui Li
- 1075 Strategy for Disease Diagnosis, Progression Prediction, Risk Group Stratification and Treatment—Case of COVID-19**  
Mauno Vihinen
- 1081 Clinical Features of 33 Cases in Children Infected With SARS-CoV-2 in Anhui Province, China—A Multi-Center Retrospective Cohort Study**  
Lan Zhang and Songming Huang
- 1088 Mask-Wearing Increased After a Government Recommendation: A Natural Experiment in the U.S. During the COVID-19 Pandemic**  
Matthew H. Goldberg, Abel Gustafson, Edward W. Maibach, Matthew T. Ballew, Parrish Bergquist, John E. Kotcher, Jennifer R. Marlon, Seth A. Rosenthal and Anthony Leiserowitz
- 1094 The COVID-19 Diagnostic Technology Landscape: Efficient Data Sharing Drives Diagnostic Development**  
Eric R. G. R. Aguiar, Jesús Navas and Luis G. C. Pacheco
- 1098 ACE/ACE2 Ratio: A Key Also in 2019 Coronavirus Disease (Covid-19)?**  
Pasquale Pagliaro and Claudia Penna
- 1103 Too Much Information: Assessing Privacy Risks of Contact Trace Data Disclosure on People With COVID-19 in South Korea**  
Gyuwon Jung, Hyunsoo Lee, Auk Kim and Uichin Lee
- 1116 Nasopharyngeal Swabs Are More Sensitive Than Oropharyngeal Swabs for COVID-19 Diagnosis and Monitoring the SARS-CoV-2 Load**  
Huan Wang, Qian Liu, Jing Hu, Min Zhou, Mu-qing Yu, Kai-yan Li, Dong Xu, Yao Xiao, Jun-yi Yang, Yan-jun Lu, Feng Wang, Ping Yin and Shu-yun Xu
- 1124 Leucocyte Subsets Effectively Predict the Clinical Outcome of Patients With COVID-19 Pneumonia: A Retrospective Case-Control Study**  
Jiahua Gan, Jingjing Li, Shusheng Li and Chunguang Yang
- 1131 Spread and Impact of COVID-19 in China: A Systematic Review and Synthesis of Predictions From Transmission-Dynamic Models**  
Yi-Fan Lin, Qibin Duan, Yiguo Zhou, Tanwei Yuan, Peiyang Li, Thomas Fitzpatrick, Leiwen Fu, Anping Feng, Ganfeng Luo, Yuewei Zhan, Bowen Liang, Song Fan, Yong Lu, Bingyi Wang, Zhenyu Wang, Heping Zhao, Yanxiao Gao, Meijuan Li, Dahui Chen, Xiaoting Chen, Yunlong Ao, Linghua Li, Weiping Cai, Xiangjun Du, Yuelong Shu and Huachun Zou
- 1142 Metapopulation Network Models for Understanding, Predicting, and Managing the Coronavirus Disease COVID-19**  
Daniela Calvetti, Alexander P. Hoover, Johnie Rose and Erkki Somersalo
- 1158 Intoxication With Endogenous Angiotensin II: A COVID-19 Hypothesis**  
Adonis Sfera, Carolina Osorio, Nyla Jafri, Eddie Lee Diaz and Jose E. Campo Maldonado



- 1170 *Quercetin and Vitamin C: An Experimental, Synergistic Therapy for the Prevention and Treatment of SARS-CoV-2 Related Disease (COVID-19)***  
Ruben Manuel Luciano Colunga Biancatelli, Max Berrill, John D. Catravas and Paul E. Marik
- 1181 *Strongly Heterogeneous Transmission of COVID-19 in Mainland China: Local and Regional Variation***  
Yuke Wang and Peter Teunis
- 1192 *Re-positive Cases of Nucleic Acid Tests in Discharged Patients With COVID-19: A Follow-Up Study***  
Xi-Min Qiao, Xiao-Feng Xu, Hao Zi, Guo-Xiong Liu, Bing-Hui Li, Xiang Du, Zhi-Hai Tian, Xiao-Ying Liu, Li-Sha Luo and Xiao Wang
- 1200 *Nanobodies: Prospects of Expanding the Gamut of Neutralizing Antibodies Against the Novel Coronavirus, SARS-CoV-2***  
Rocktotpal Konwarh
- 1206 *Systematic Review and Meta-Analysis of Sex-Specific COVID-19 Clinical Outcomes***  
Thushara Galbadage, Brent M. Peterson, Joseph Awada, Alison S. Buck, Danny A. Ramirez, Jason Wilson and Richard S. Gunasekera
- 1221 *Liver Injury in Critically Ill and Non-critically Ill COVID-19 Patients: A Multicenter, Retrospective, Observational Study***  
Saiping Jiang, Rongrong Wang, Lu Li, Dongsheng Hong, Renping Ru, Yuefeng Rao, Jing Miao, Na Chen, Xiuhua Wu, Ziqi Ye, Yunzhen Hu, Minghua Xie, Minjuan Zuo, Xiaoyang Lu, Yunqing Qiu and Tingbo Liang
- 1231 *Cotton-Tipped Plastic Swabs for SARS-CoV-2 RT-qPCR Diagnosis to Prevent Supply Shortages***  
Byron Freire-Paspuel, Patricio Vega-Mariño, Alberto Velez, Paulina Castillo, Eliana Elizabeth Gomez-Santos, Marilyn Cruz and Miguel Angel Garcia-Bereguain
- 1235 *Vitamin D Supplementation: A Potential Approach for Coronavirus/COVID-19 Therapeutics?***  
John F. Arboleda and Silvio Urcuqui-Inchima
- 1239 *Targeting the NLRP3 Inflammasome in Severe COVID-19***  
Tracey L. Freeman and Talia H. Swartz
- 1251 *Children Infected With SARS-CoV-2 From Family Clusters***  
Dan Sun, Feng Zhu, Cheng Wang, Jing Wu, Jie Liu, Xue Chen, Zhisheng Liu, Zubo Wu, Xiaoxia Lu, Jiehui Ma, Hua Peng and Han Xiao
- 1259 *Human Sialome and Coronavirus Disease-2019 (COVID-19) Pandemic: An Understated Correlation?***  
Daniela Morniroli, Maria Lorella Gianni, Alessandra Consales, Carlo Pietrasanta and Fabio Mosca
- 1263 *Targeting the Immune System for Pulmonary Inflammation and Cardiovascular Complications in COVID-19 Patients***  
Serena Colafrancesco, Rossana Scrivo, Cristiana Barbati, Fabrizio Conti and Roberta Priori
- 1281 *Biocides and Novel Antimicrobial Agents for the Mitigation of Coronaviruses***  
Govindaraj Dev Kumar, Abhinav Mishra, Laurel Dunn, Anna Townsend, Ikechukwu Chukwuma Oguadinma, Kelly R. Bright and Charles P. Gerba

- 1293 Entropy-Based Pandemics Forecasting**  
Umberto Lucia, Thomas S. Deisboeck and Giulia Grisolia
- 1300 Immune and Metabolic Signatures of COVID-19 Revealed by Transcriptomics Data Reuse**  
Luiz G. Gardinassi, Camila O. S. Souza, Helioswilton Sales-Campos and Simone G. Fonseca
- 1308 Chest Computed Tomography and Lung Ultrasound Findings in COVID-19 Pneumonia: A Pocket Review for Non-radiologists**  
Davide Pata, Piero Valentini, Cristina De Rose, Rita De Santis, Rosa Morello and Danilo Buonsenso
- 1313 Prealbumin as a Predictor of Prognosis in Patients With Coronavirus Disease 2019**  
Ying Luo, Ying Xue, Liyan Mao, Xu Yuan, Qun Lin, Guoxing Tang, Huijuan Song, Feng Wang and Ziyong Sun
- 1322 A Low Viral Dose in COVID-19 Patient: A Case Report**  
Yajuan Li, Xianwei Hu, Youhui Tu, Tao Wu, Bo Wang, Huan Ma, Weihong Zeng, Dan Zhao, Hylemariam Mihiretie Mengist, Arnaud John Kombe Kombe, Meijuan Zheng, Yuanhong Xu and Tengchuan Jin
- 1328 Severe COVID-19: NLRP3 Inflammasome Dysregulated**  
Daan F. van den Berg and Anje A. te Velde
- 1334 Semantic and Geographical Analysis of COVID-19 Trials Reveals a Fragmented Clinical Research Landscape Likely to Impair Informativeness**  
Giulia Tini, Bruno Achutti Duso, Federica Bellerba, Federica Corso, Sara Gandini, Saverio Minucci, Pier Giuseppe Pelicci and Luca Mazzarella
- 1341 The (In)Appropriateness of the WAR Metaphor in Response to SARS-CoV-2: A Rapid Analysis of Donald J. Trump's Rhetoric**  
Benjamin R. Bates
- 1353 Kerala, India's Front Runner in Novel Coronavirus Disease (COVID-19)**  
S. Udhaya Kumar, D. Thirumal Kumar, R. Siva and C. George Priya Doss
- 1357 Clinical Use of Short-Course and Low-Dose Corticosteroids in Patients With Non-severe COVID-19 During Pneumonia Progression**  
Zhiliang Hu, Yanling Lv, Chuanjun Xu, Wenkui Sun, Wei Chen, Zhihang Peng, Chen Chen, Xiang Cui, Damin Jiao, Cong Cheng, Yun Chi, Hongxia Wei, Chunmei Hu, Yi Zeng, Xia Zhang and Yongxiang Yi
- 1365 Analysis of ACE2 Gene-Encoded Proteins Across Mammalian Species**  
Ying Cao, Yeping Sun, Xiaodong Tian, Zhihua Bai, Yue Gong, Jianxun Qi, Di Liu, Wenjun Liu and Jing Li
- 1371 Cell-Mediated Immune Responses to COVID-19 Infection**  
Amélie Guihot, Elena Litvinova, Brigitte Autran, Patrice Debré and Vincent Vieillard
- 1379 COVID-19 Transmission Within a Family Cluster in Yancheng, China**  
Hongming Zhang, Runzhe Chen, Jibei Chen and Baoan Chen
- 1383 Non-pharmaceutical Interventions for Pandemic COVID-19: A Cross-Sectional Investigation of US General Public Beliefs, Attitudes, and Actions**  
Bella Nichole Kantor and Jonathan Kantor

- 1389 Medium Term Follow-Up of 337 Patients With Coronavirus Disease 2019 (COVID-19) in a Fangcang Shelter Hospital in Wuhan, China**  
Nao Yan, Wei Wang, Yongzhe Gao, Junhui Zhou, JiuHong Ye, Zhipeng Xu, Jing Cao and Junjian Zhang
- 1396 Current Findings Regarding Natural Components With Potential Anti-2019-nCoV Activity**  
Jin Zhou and Jie Huang
- 1409 Targeting GM-CSF in COVID-19 Pneumonia: Rationale and Strategies**  
Aldo Bonaventura, Alessandra Vecchié, Tisha S. Wang, Elinor Lee, Paul C. Cremer, Brenna Carey, Prabalini Rajendram, Kristin M. Hudock, Leslie Korbee, Benjamin W. Van Tassell, Lorenzo Dagna and Antonio Abbate
- 1419 Community Drivers Affecting Adherence to WHO Guidelines Against COVID-19 Amongst Rural Ugandan Market Vendors**  
Ibe Michael Usman, Fred Ssempijja, Robinson Ssebuufu, Ann Monima Lemuel, Victor Bassey Archibong, Emmanuel Tiyo Ayikobua, Joshua Ojodale Aruwa, Stellamaris Kembabazi, Eric Simidi Kegoye, John Tabakwot Ayuba, Olatayo Segun Okeniran, Isaac Echoru, Azeez Adeoye, Regan Mujinya, Viola Nankya and Keneth Iceland Kasozi
- 1432 Severe Acute Respiratory Syndrome Coronavirus 2: From Gene Structure to Pathogenic Mechanisms and Potential Therapy**  
Jun Wu, Xiaohui Yuan, Bing Wang, Rui Gu, Wei Li, Xuemei Xiang, Lijun Tang and Hongyu Sun
- 1445 COVID-19 Coronavirus Vaccine Design Using Reverse Vaccinology and Machine Learning**  
Edison Ong, Mei U Wong, Anthony Huffman and Yongqun He
- 1458 Prevention and Control of COVID-19 Infection in a Chinese Mental Health Center**  
Mi Yang, Hongming Wang, Zhi Li, Qiang Zhang, Xin Liu, Manxi He and Shan Gao
- 1465 Survival-Convolution Models for Predicting COVID-19 Cases and Assessing Effects of Mitigation Strategies**  
Qinxia Wang, Shanghong Xie, Yuanjia Wang and Donglin Zeng
- 1473 A Perspective on Emerging Therapeutic Interventions for COVID-19**  
Muhammad Torequl Islam, Md. Nasiruddin, Ishaq N. Khan, Siddhartha Kumar Mishra, Md. Kudrat-E-Zahan, Thoufiqul Alam Riaz, Eunus S. Ali, M. Safiur Rahman, Mohammad S. Mubarak, Miquel Martorell, William C. Cho, Daniela Calina, Anca Oana Docea and Javad Sharifi-Rad
- 1488 False Positive COVID-19 Antibody Test in a Case of Granulomatosis With Polyangiitis**  
Argyrios Tzouvelekis, Theodoros Karampitsakos, Anastasia Krompa, Evangelos Markozannes and Demosthenes Bouras
- 1492 Progress in the Research and Development of Anti-COVID-19 Drugs**  
Lianzhou Huang, Yuanqiu Chen, Ji Xiao, Weisheng Luo, Feng Li, Yuan Wang, Yiliang Wang and Yifei Wang
- 1500 Pregnancy, Viral Infection, and COVID-19**  
Ricardo Wesley Alberca, Nátalli Zanete Pereira, Luanda Mara Da Silva Oliveira, Sarah Cristina Gozzi-Silva and Maria Notomi Sato

- 1512 *Novel Coronavirus Pneumonia Treatment With Traditional Chinese Medicine: Response Philosophy in Another Culture***  
Zhuman Li, Chuangchuang Han, Huihong Huang, Zhijun Guo and Feng Xu
- 1515 *Recent Advancements in the Diagnosis, Prevention, and Prospective Drug Therapy of COVID-19***  
Waquar Ahsan, Hassan A. Alhazmi, Kuldeep Singh Patel, Bharti Mangla, Mohammed Al Bratty, Shamama Javed, Asim Najmi, Muhammad Hadi Sultan, Hafiz A. Makeen, Asaad Khalid, Syam Mohan, Manal M. E. Taha and Shahnaz Sultana
- 1529 *A Hypothesis for the Possible Role of Zinc in the Immunological Pathways Related to COVID-19 Infection***  
Ander Mayor-Ibarguren, Carmen Busca-Arenzana and Ángel Robles-Marhuenda
- 1537 *Clinical Characteristics and Eosinophils in Young SARS-CoV-2-Positive Chinese Travelers Returning to Shanghai***  
Juan Yang, Xiaohui Zhao, Xueyuan Liu, Wanju Sun, Longzhu Zhou, Yongbing Wang and Haijing Sui
- 1544 *Evidence That Higher Temperatures Are Associated With a Marginally Lower Incidence of COVID-19 Cases***  
Anne Meyer, Rohan Sadler, Céline Faverjon, Angus Robert Cameron and Melanie Bannister-Tyrrell
- 1551 *Cytokine Storm in COVID-19: The Current Evidence and Treatment Strategies***  
Yujun Tang, Jiajia Liu, Dingyi Zhang, Zhenghao Xu, Jinjun Ji and Chengping Wen
- 1564 *Identification of SARS-CoV-2 Cell Entry Inhibitors by Drug Repurposing Using in silico Structure-Based Virtual Screening Approach***  
Shweta Choudhary, Yashpal S. Malik and Shailly Tomar
- 1578 *Designing Multi-Epitope Vaccines to Combat Emerging Coronavirus Disease 2019 (COVID-19) by Employing Immuno-Informatics Approach***  
Anam Naz, Fatima Shahid, Tariq Tahir Butt, Faryal Mehwish Awan, Amjad Ali and Arif Malik
- 1591 *Transmission Routes Analysis of SARS-CoV-2: A Systematic Review and Case Report***  
Huanjie Li, Yangyang Wang, Mingyu Ji, Fengyan Pei, Qianqian Zhao, Yuning Zhou, Yatian Hong, Shuyi Han, Jun Wang, Qingxi Wang, Qiang Li and Yunshan Wang
- 1602 *nCOVID-19 Pandemic: From Molecular Pathogenesis to Potential Investigational Therapeutics***  
Md. Tanvir Kabir, Md. Sahab Uddin, Md. Farhad Hossain, Jawaher A. Abdulhakim, Md. Asrafal Alam, Ghulam Md Ashraf, Simona G. Bungau, May N. Bin-Jumah, Mohamed M. Abdel-Daim and Lotfi Aleya
- 1625 *Could the Induction of Trained Immunity by  $\beta$ -Glucan Serve as a Defense Against COVID-19?***  
Anne Geller and Jun Yan

**1636 Acceptance of a COVID-19 Vaccine in Southeast Asia: A Cross-Sectional Study in Indonesia**

Harapan Harapan, Abram L. Wagner, Amanda Yufika, Wira Winardi, Samsul Anwar, Alex Kurniawan Gan, Abdul Malik Setiawan, Yogambigai Rajamoorthy, Hizir Sofyan and Mudatsir Mudatsir

**1644 Extensive Testing May Reduce COVID-19 Mortality: A Lesson From Northern Italy**

Mauro Di Bari, Daniela Balzi, Giulia Carreras and Graziano Onder

**1649 Administration of Immunoglobulins in SARS-CoV-2-Positive Patient Is Associated With Fast Clinical and Radiological Healing: Case Report**

Novella Carannante, Giuseppe Fiorentino, Antonio Corcione, Raffaele Di Sarno, Micaela Spatarella, Nicola Maturo, Fiorentino Fragranza and Pierpaolo Di Micco

**1653 Early Warning Indicators of Severe COVID-19: A Single-Center Study of Cases From Shanghai, China**

Yiming Lu, Kuo Sun, Shanshan Guo, Junjie Wang, An Li, Xuli Rong, Tingfang Wang, Yan Shang, Wenjun Chang and Sheng Wang

**1662 Country-Wise Forecast Model for the Effective Reproduction Number  $R_t$  of Coronavirus Disease**

David Medina-Ortiz, Sebastián Contreras, Yasna Barrera-Saavedra, Gabriel Cabas-Mora and Álvaro Olivera-Nappa



# The Malnutritional Status of the Host as a Virulence Factor for New Coronavirus SARS-CoV-2

Matteo Briguglio<sup>1\*</sup>, Fabrizio Ernesto Pregliasco<sup>2,3</sup>, Giovanni Lombardi<sup>4,5</sup>, Paolo Perazzo<sup>6</sup> and Giuseppe Banfi<sup>1,7</sup>

<sup>1</sup> IRCCS Orthopedic Institute Galeazzi, Scientific Direction, Milan, Italy, <sup>2</sup> Health Management, IRCCS Orthopedic Institute Galeazzi, Milan, Italy, <sup>3</sup> Department of Biomedical Sciences for Health, University of Milan, Milan, Italy, <sup>4</sup> Laboratory of Experimental Biochemistry and Molecular Biology, IRCCS Orthopedic Institute Galeazzi, Milan, Italy, <sup>5</sup> Department of Athletics, Strength and Conditioning, Poznań University of Physical Education, Poznań, Poland, <sup>6</sup> Post-operative Intensive Care Unit & Anesthesia, IRCCS Orthopedic Institute Galeazzi, Milan, Italy, <sup>7</sup> Faculty of Medicine and Surgery, Vita-Salute San Raffaele University, Milan, Italy

**Keywords:** nutritional status, coronavirus, SARS-CoV-2, COVID-19, infections, virulence, host pathogen interactions, quality of health care

## THE SPILL OUT OF SARS-CoV-2

An outbreak of viral pneumonia was reported in Wuhan, China, at the end of December 2019, and subsequent sample analyses discovered the involvement of a new strain of coronavirus (SARS-CoV-2), which belongs to the same family of single-stranded enveloped RNA viruses that caused the emergences of SARS-CoV in 2003 and MERS-CoV in 2012. Symptoms of COVID-19 (SARS-CoV-2 syndrome) may occur within 2–14 days after exposure and can lead to difficulties in cilium beating of airway cells and to alveolar damage (1). Infected patients experience mild to severe manifestations, such as fever, dry cough, dyspnoea, abdominal pain, and diarrhea. Most cases resolve rapidly, but the infection can still be fatal in about 3% of cases (2). Much like MERS or the coronavirus that infects pigs, the enteric affections can be prominent (3, 4), possibly leading to the loss of absorptive potential. Just a few weeks after its discovery, the COVID-19 has been considered a serious worldwide threat. At the time of writing, Italy is the worst-hit country with 97,689 confirmed cases and 10,781 total deaths (WHO COVID-19 Situation report 70, 30 March 2020). Preliminary data suggest that male older adults and subjects with immune dysfunctions might be more susceptible to the worse viral disease, but there is a need to further investigate the virulence factors. One of the factors most discussed is the malnutritional status of the host, but most of the beliefs are anecdotal. On the other hand, strong evidence supports the notion that any infection outcome is highly dependent on the nutritional status of the host since viruses subject the host's body to a considerable energetic effort to sustain costly defenses. If a previous malnutritional status exists, or if no nutritional care is provided, the host easily encounters the emptying of body reservoirs with increased harm caused by the virus. A possible link between the nutritional status of the host, the virulence of SARS-CoV-2, and the clinical outcome of COVID-19 needs to be discussed.

## THE HOST ABILITIES AGAINST INFECTIONS

A distinction should be made between the susceptibility to developing a symptomatic infection, from now on referred to as “first-line host ability,” and the fighting potential, referred to as “second-line host ability.” From the perspective of infectious diseases, the first-line host ability is expressed by its immunocompetence, which is in turn uttered by the nutrient intake-requirement balance.

### OPEN ACCESS

#### Edited by:

Zisis Kozlakidis,  
International Agency for Research on  
Cancer (IARC), France

#### Reviewed by:

Andreas Nüssler,  
Tübingen University  
Hospital, Germany

#### \*Correspondence:

Matteo Briguglio  
matteo.briguglio@grupposandonato.it

#### Specialty section:

This article was submitted to  
Infectious Diseases - Surveillance,  
Prevention and Treatment,  
a section of the journal  
Frontiers in Medicine

**Received:** 20 March 2020

**Accepted:** 03 April 2020

**Published:** 23 April 2020

#### Citation:

Briguglio M, Pregliasco FE,  
Lombardi G, Perazzo P and Banfi G  
(2020) The Malnutritional Status of the  
Host as a Virulence Factor for New  
Coronavirus SARS-CoV-2.  
*Front. Med.* 7:146.  
doi: 10.3389/fmed.2020.00146

A malnutritional status refers to any balance deviation, including the general excess, insufficiency, or single-nutrient deficits. The second-line host ability is expressed by the endurance or ability to persist in fighting the infection. For SARS-CoV-2, it can be assumed that the healthier is the nutritional status of the host, the higher are the first-line host abilities, the lower is the susceptibility to COVID-19, the lower is the virulence of SARS-CoV-2, and, thus, the longer the host will endure in the fight. This transitive relation is not necessarily assumable for all pathogens. Concerning parasitic infections, well-nourished subjects may offer a wealthier environment to developing parasites than malnourished individuals (5), but they can also afford investments to endure in the fight, still having the upper hand on the infection outcome. Whatever the nature of the susceptibility to viral infections, second-line host abilities are based not only on the ability to support an adequate immune response but rely also on the body's ability to support an extensive controlled catabolic cytokine flow. Once infected, the nutritional reservoirs have been shown to influence outcomes in many diseases, comprising the immunodeficiency virus, the influenza virus, or pneumonia (6, 7). The within-host reservoirs depend on the external environment (8); the highest resources should exist in hosts living in the wealthiest environments. Regrettably, even the wealthiest countries present high rates of deficiency syndromes.

## THE HOST REACTIONS AGAINST SARS-CoV-2

Both first- and second-line host abilities are necessary to heal from SARS-CoV-2 infection. Once the virus gets inside the airways through respiratory droplets, it infects local cells and evokes the host immune response. Mild symptoms of COVID-19 may be triggered by a local inflammation limited to the lungs that should resolve quickly. Asymptomatic individuals have been reported to have no high fever (no increased expenditure) and no SARS-CoV-2-derived gastrointestinal symptoms that could have affected dietary intakes (9). The immunocompetent host response in non-severe cases recruits immune cell populations, such as CD4/CD8 T cells and antibody-secreting cells together with specific immunoglobulin (Ig)M and IgG SARS-CoV-2-binding antibodies (10). Basic treatments comprise intravenous antibiotics, antiviral therapy, antifungal medications, systemic glucocorticoids, and interferon. In cases with comorbid conditions, such as cardiovascular diseases and diabetes (11), there may be a basal immune dysfunction since the elderly and sick are often malnourished. If the immunoincompetence fails to control the SARS-CoV-2 or the virus replicates faster than expected, a severe inflammatory condition then arises and spreads to other organs together with the virus. Worsened patients show lymphopenia, cytokine storm (12), and multiple organ failure (13). These biochemical signs together with the decrease in CD4 T cells are a common feature in patients with COVID-19 and might be a critical virulence factor (14). The intestines may be particularly suitable for viral proliferation, as gut tropism is not unusual for coronaviruses. The host's

ability to endure may depend on energy-nutrient intakes, which may be hampered by gastrointestinal symptoms and the hypermetabolism. Higher rates of nausea, vomiting, and diarrhea were observed in severe COVID-19 patients, which appear to be more likely to have anorexia (15). The prevalence of malnutrition (probably hyponutrition) was 3% among the deceased vs. 0% among survivors (16). Healthy body reservoirs, early adaptive immune potential, and nutritional care may indeed be associated with better outcomes from COVID-19.

## THE DISABILITIES OF MALNOURISHED INDIVIDUALS DURING INFECTIONS

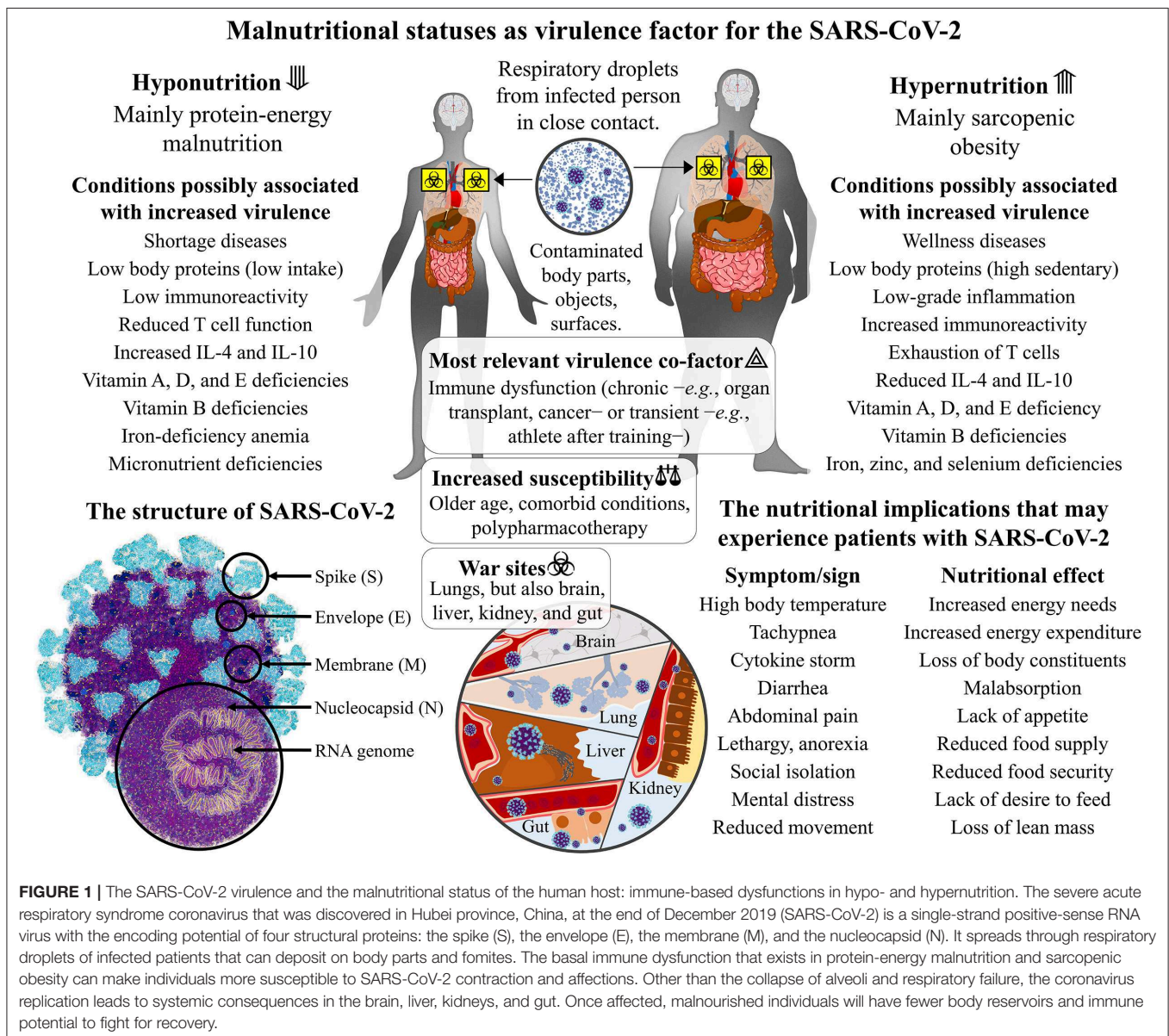
“Malnutrition is the primary cause of immunodeficiency worldwide” (17) and affects both the innate and adaptive immune responses (18) that should inhibit viral proliferation. Chronic diseases, which have been recognized as virulence factors for severe COVID-19, are often comorbid with protein-energy malnutrition (also known as disease-related malnutrition), which is known to impair immune cell activation (19, 20), thus allowing longer viral persistence and increased trafficking of inflammatory cells to lungs (21). The basal immunoincompetence (22) can be further aggravated upon infection (23). Insufficient protein intakes may lead to nutrition-related sarcopenia. The concomitant excess of adiposity has been defined as “sarcopenic obesity” and carries issues of both conditions. Increased body fat sustains a systemic low-grade inflammation, primarily because of the leptin-induced CD4 T-cell function that increases autoimmunity (24). Basal T cells are more prone to exhaustion in obese subjects (25) who may therefore be more exposed to SARS-CoV-2 proliferation, as occurs with the herpes simplex virus (26). In fact, exhausted T cells exhibit poor effector function, proliferation, and cytotoxicity (27). During the 2009 pandemic caused by the influenza A (H1N1)pdm09 virus, obesity was found to be a virulence factor for a more severe outcome (28) much like for respiratory infections (29). Micronutrient deficiencies are also a rising issue among malnourished subjects. Vitamins have a role in the proper functioning of both the innate and adaptive immune responses, with vitamin D and A being the main actors (30). For instance, vitamin D is important for the proper functioning of antibody-secreting cells (31) and vitamin A sustains T-cell proliferation (32). The immune dysfunction in hyponutritional statuses can be linked to these deficiencies alike the excess of feeding, which is often associated with a monotonous diet and therefore low in sources of vitamins. A plethora of other micronutrients is known to have a role in the immunocompetence of the host against infections, including B vitamins, vitamin C, vitamin E, iron, selenium, and zinc (33), with malnourished individuals often suffering from the most. Malnutritional statuses carry less endurance to survive from severe COVID-19. Hypermetabolism and excessive nitrogen loss are factors known to be associated with infective states, and malnourished individuals are therefore disadvantaged because of the lesser body reserves. For instance, infected mice fed with lesser proteins, iron, and zinc than the optimal requirements were

found to encounter a significant decrease in both weight and effector CD4 T cells vs. normal nourished animals (34).

### NUTRITIONAL CARE IN COVID-19

If the patient had a good nutritional status before infection, then body reserves and basal dietary intake would assure the coverage of costly immune defenses in mild conditions. If a malnutritional status was present, which is very common among older adults, then increased requirements should be provided since the infection is expected to be protracted (35). Mild cases might experience a loss of appetite often accompanied by insomnia, nausea, vomiting, and reduced oral intakes, thus further compromising the basal poor nutritional. Even subacute malnourished patients are more prone to adverse events

than healthy counterparts upon hospital admission (36). Once mechanical ventilation, extracorporeal membrane oxygenation, and renal-replacement therapy have been introduced, parenteral nutrition is the sole option. Severe cases with fever have increased energy expenditure and requirements for each degree of temperature increase. The usage of muscle-derived amino acids for immune protein synthesis increases whole-body glucose and nitrogen excretion, with a significant energy cost of immune upregulation (37). Unfortunately, the increased adiposity of obese individuals is not effectively used during infections (38), and the breakdown of the already poor muscle mass can have severe consequences. Similar metabolic consequences are seen in older trauma patients, with the malnourished subjects being the most at risk of adverse clinical outcomes (39). If energy and protein requirements are met, then the emptying of body





reservoirs may be avoided, and the immune response may be sustained. Once full-blown, COVID-19 patients should be supported with proper nutrition aimed at delivering adequate proteins (1.5–2.0 g/kg/day likely needed), energy (105–160 kJ/kg/day or 25–40 kcal/kg/day), vitamins, and trace elements. Nutrition should be titrated up to meet higher requirements because the delivery of the highest energy during the initial phase may be counterproductive. Guidelines for polymorbid patients should be followed (40–42). Partial isocaloric replacement of carbohydrates with lipids may be considered to reduce the production of CO<sub>2</sub> by 30% per caloric unit (43).

## CONCLUSION

In the current pandemic panorama of SARS-CoV-2, the link between nutrition and virulence takes a predictable turn. On one hand, many opportunists boast dietary plans against SARS-CoV-2, and, on the other hand, there is the sellout of dietary supplements that boost the immune system. In Italy, many instances of fake news have circulated on social networks, and many pharmacies have exposed signs that state: “Masks sold-out but vitamin C available.” In these times of fear and confusion, speculations should be disciplined. Nonetheless, a greater understanding of the link between nutrition and SARS-CoV-2 is needed, as the pathogen fitness may also depend on the host available resources (44). Future studies should focus on the transmission potential of malnutritional statuses. In the past, these conditions were suggested to negatively influence the transmission of alphaviruses to other hosts (45). Since most of infected cases are asymptomatic, the spreading of the virus is much easier than the previous coronaviruses (46). Yet, the risk of contracting SARS-CoV-2 does not depend on the individual's nutritional status but on the degree of contact with

the pathogen. Whether the coronavirus exposure develops into a true infection might contrariwise depend on the individual's first-line abilities, and, regrettably, malnutrition is a common occurrence that afflicts many older adults in China (47) and Italy (48), both having been heavily afflicted by the highest number of deaths. It is clear that the segment of population most at risk of SARS-CoV-2 infection is the elderly, with frailty (49) and older age (50) being well-known predictors of a negative outcome in acute care settings. Intensive clinical monitoring at admission with subsequent tailored nutritional care is needed for COVID-19 patients, especially those with co-existing chronic conditions or medications that could further aggravate the nutritional status (51). To conclude, there are several main nutritional issues to consider when fighting COVID-19 (see **Figure 1** for details). A malnutritional status is associated with immune dysfunction. Malnourished individuals may be more susceptible to SARS-CoV-2 infection. Subjects with COVID-19 often become malnourished. Nutritional support is vital in severe COVID-19 patients.

## AUTHOR CONTRIBUTIONS

MB formulated the hypothesis and wrote the first draft of the manuscript. FP, GL, PP, and GB revised the first draft and contributed to manuscript sections. All authors contributed to manuscript revision, read, and approved the submitted version.

## ACKNOWLEDGMENTS

None that interests colleagues, institutions, or agencies in supporting this hypothesis. Yet all authors thank all the health workers and volunteers in Italy at the front lines of the fight against this SARS-CoV-2.

## REFERENCES

- Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med.* (2020) 382:727–33. doi: 10.1056/NEJMoa2001017
- Guan W-J, Ni Z-Y, Hu Y, Liang W-H, Ou C-Q, He J-X, et al. Clinical characteristics of 2019 novel coronavirus infection in China. *N Engl J Med.* (2020). doi: 10.1056/NEJMoa2002032
- Zhou J, Huang F, Hua X, Cui L, Zhang W, Shen Y, et al. Inhibition of porcine transmissible gastroenteritis virus (TGEV) replication in mini-pigs by shRNA. *Virus Res.* (2010) 149:51–5. doi: 10.1016/j.virusres.2009.12.012
- Mao R, Liang J, Shen J, Ghosh S, Zhu L-R, Yang H, et al. Implications of COVID-19 for patients with pre-existing digestive diseases. *Lancet Gastroenterol Hepatol.* (2020). doi: 10.1016/S2468-1253(20)30076-5. [Epub ahead of print].
- Cornet S, Sorci G. Parasite virulence when the infection reduces the host immune response. *Proc Biol Sci.* (2010) 277:1929–35. doi: 10.1098/rspb.2010.0138
- Chandra RK. Nutrition, immunity and infection: from basic knowledge of dietary manipulation of immune responses to practical application of ameliorating suffering and improving survival. *Proc Natl Acad Sci USA.* (1996) 93:14304–7. doi: 10.1073/pnas.93.25.14304
- Cressler CE, Nelson WA, Day T, McCauley E. Disentangling the interaction among host resources, the immune system and pathogens. *Ecol Lett.* (2014) 17:284–93. doi: 10.1111/ele.12229
- Mideo N, Alizon S, Day T. Linking within- and between-host dynamics in the evolutionary epidemiology of infectious diseases. *Trends Ecol Evol.* (2008) 23:511–7. doi: 10.1016/j.tree.2008.05.009
- Hu Z, Song C, Xu C, Jin G, Chen Y, Xu X, et al. Clinical characteristics of 24 asymptomatic infections with COVID-19 screened among close contacts in Nanjing, China. *Sci China Life Sci.* (2020). doi: 10.1007/s11427-020-1661-4. [Epub ahead of print].
- Thevarajan I, Nguyen THO, Koutsakos M, Druce J, Caly L, van de Sandt CE, et al. Breadth of concomitant immune responses prior to patient recovery: a case report of non-severe COVID-19. *Nat Med.* (2020) 16:1–3. doi: 10.1038/s41591-020-0819-2
- Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA.* (2020). doi: 10.1001/jama.2020.1585. [Epub ahead of print].
- Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet.* (2020) 395:497–506. doi: 10.1016/S0140-6736(20)30183-5
- Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet.* (2020) 395:507–13. doi: 10.1016/S0140-6736(20)30211-7
- Zhang C, Shi L, Wang FS. Liver injury in COVID-19: management and challenges. *Lancet Gastroenterol Hepatol.* (2020) 5:428–30. doi: 10.1016/S2468-1253(20)30057-1

15. Mo P, Xing Y, Xiao Y, Deng L, Zhao Q, Wang H, et al. Clinical characteristics of refractory COVID-19 pneumonia in Wuhan, China. *Clin Infect Dis.* (2020). doi: 10.1093/cid/ciaa270. [Epub ahead of print].
16. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med.* (2020). doi: 10.1016/S2213-2600(20)30079-5
17. Katona P, Katona-Apte J. The interaction between nutrition and infection. *Clin Infect Dis.* (2008) 46:1582–8. doi: 10.1086/587658
18. Alwarawrah Y, Kiernan K, MacIver NJ. Changes in nutritional status impact immune cell metabolism and function. *Front Immunol.* (2018) 9:1055. doi: 10.3389/fimmu.2018.01055
19. Wing EJ, Magee DM, Barczynski LK. Acute starvation in mice reduces the number of T cells and suppresses the development of T-cell-mediated immunity. *Immunology.* (1988) 63:677–82.
20. Gerriets VA, MacIver NJ. Role of T cells in malnutrition and obesity. *Front Immunol.* (2014) 5:379. doi: 10.3389/fimmu.2014.00379
21. Taylor AK, Cao W, Vora KP, De La Cruz J, Shieh WJ, Zaki SR, et al. Protein energy malnutrition decreases immunity and increases susceptibility to influenza infection in mice. *J Infect Dis.* (2013) 207:501–10. doi: 10.1093/infdis/jis527
22. Gonzalez-Martinez H, Rodriguez L, Najera O, Cruz D, Miliar A, Dominguez A, et al. Expression of cytokine mRNA in lymphocytes of malnourished children. *J Clin Immunol.* (2008) 28:593–9. doi: 10.1007/s10875-008-9204-5
23. Najera O, Gonzalez C, Toledo G, Lopez L, Ortiz R. Flow cytometry study of lymphocyte subsets in malnourished and well-nourished children with bacterial infections. *Clin Diagn Lab Immunol.* (2004) 11:577–80. doi: 10.1128/CDLI.11.3.577-580.2004
24. Procaccini C, De Rosa V, Galgani M, Carbone F, Cassano S, Greco D, et al. Leptin-induced mTOR activation defines a specific molecular and transcriptional signature controlling CD4+ effector T cell responses. *J Immunol.* (2012) 189:2941–53. doi: 10.4049/jimmunol.1200935
25. Kado T, Nawaz A, Takikawa A, Usui I, Tobe K. Linkage of CD8(+) T cell exhaustion with high-fat diet-induced tumorigenesis. *Sci Rep.* (2019) 9:12284. doi: 10.1038/s41598-019-48678-0
26. Hoshino Y, Pesnick L, Cohen JI, Straus SE. Rates of reactivation of latent herpes simplex virus from mouse trigeminal ganglia *ex vivo* correlate directly with viral load and inversely with number of infiltrating CD8+ T cells. *J Virol.* (2007) 81:8157–64. doi: 10.1128/JVI.00474-07
27. Schietinger A, Greenberg PD. Tolerance and exhaustion: defining mechanisms of T cell dysfunction. *Trends Immunol.* (2014) 35:51–60. doi: 10.1016/j.it.2013.10.001
28. Louie JK, Acosta M, Samuel MC, Schechter R, Vugia DJ, Harriman K, et al. A novel risk factor for a novel virus: obesity and 2009 pandemic influenza A (H1N1). *Clin Infect Dis.* (2011) 52:301–12. doi: 10.1093/cid/ciq152
29. Milner JJ, Beck MA. The impact of obesity on the immune response to infection. *Proc Nutr Soc.* (2012) 71:298–306. doi: 10.1017/S0029665112000158
30. Mora JR, Iwata M, von Andrian UH. Vitamin effects on the immune system: vitamins A and D take centre stage. *Nat Rev Immunol.* (2008) 8:685–98. doi: 10.1038/nri2378
31. Shirakawa AK, Nagakubo D, Hieshima K, Nakayama T, Jin Z, Yoshie O. 1,25-dihydroxyvitamin D3 induces CCR10 expression in terminally differentiating human B cells. *J Immunol.* (2008) 180:2786–95. doi: 10.4049/jimmunol.180.5.2786
32. Ertesvag A, Engedal N, Naderi S, Blomhoff HK. Retinoic acid stimulates the cell cycle machinery in normal T cells: involvement of retinoic acid receptor-mediated IL-2 secretion. *J Immunol.* (2002) 169:5555–63. doi: 10.4049/jimmunol.169.10.5555
33. Gombar AF, Pierre A, Maggini S. A review of micronutrients and the immune system-working in harmony to reduce the risk of infection. *Nutrients.* (2020) 12:236. doi: 10.3390/nu12010236
34. Pilotos J, Smith MR, Johnson CM, Campbell L, Ibitokou S, Stephens R, et al. Malnutrition decreases both effector and memory CD4T cells in malaria infection. *J Immunol.* (2018) 200(Suppl.):52.39.
35. Mahalingam M, Moore JX, Donnelly JP, Safford MM, Wang HE. Frailty Syndrome and Risk of Sepsis in the REasons for Geographic And Racial Differences in Stroke (REGARDS) Cohort. *J Intensive Care Med.* (2019) 34:292–300. doi: 10.1177/0885066617715251
36. Charlton K, Nichols C, Bowden S, Milosavljevic M, Lambert K, Barone L, et al. Poor nutritional status of older subacute patients predicts clinical outcomes and mortality at 18 months of follow-up. *Eur J Clin Nutr.* (2012) 66:1224–8. doi: 10.1038/ejcn.2012.130
37. Klasing KC. Nutritional aspects of leukocytic cytokines. *J Nutr.* (1988) 118:1436–46. doi: 10.1093/jn/118.12.1436
38. Berclaz PY, Benedek C, Jequier E, Schutz Y. Changes in protein turnover and resting energy expenditure after treatment of malaria in Gambian children. *Pediatr Res.* (1996) 39:401–9. doi: 10.1203/00006450-199603000-00005
39. Ihle C, Freude T, Bahrs C, Zehendner E, Braunsberger J, Biesalski HK, et al. Malnutrition - An underestimated factor in the inpatient treatment of traumatology and orthopedic patients: a prospective evaluation of 1055 patients. *Injury.* (2017) 48:628–36. doi: 10.1016/j.injury.2017.01.036
40. Gomes F, Schuetz P, Bounoure L, Austin P, Ballesteros-Pomar M, Cederholm T, et al. ESPEN guidelines on nutritional support for polymorbid internal medicine patients. *Clin Nutr.* (2018) 37:336–53. doi: 10.1016/j.clnu.2017.06.025
41. Singer P, Blaser AR, Berger MM, Alhazzani W, Calder PC, Casaer MP, et al. ESPEN guideline on clinical nutrition in the intensive care unit. *Clin Nutr.* (2019) 38:48–79. doi: 10.1016/j.clnu.2018.08.037
42. Murthy S, Gomersall CD, Fowler RA. Care for critically ill patients with COVID-19. *JAMA.* (2020). doi: 10.1001/jama.2020.3633. [Epub ahead of print].
43. Askanazi J, Nordenstrom J, Rosenbaum SH, Elwyn DH, Hyman AI, Carpenter YA, et al. Nutrition for the patient with respiratory failure: glucose vs. fat. *Anesthesiology.* (1981) 54:373–7. doi: 10.1097/0000542-198105000-00005
44. Pike VL, Lythgoe KA, King KC. On the diverse and opposing effects of nutrition on pathogen virulence. *Proc Biol Sci.* (2019) 286:20191220. doi: 10.1098/rspb.2019.1220
45. Weger-Lucarelli J, Carrau L, Levi LI, Rezelj V, Vallet T, Blanc H, et al. Host nutritional status affects alphavirus virulence, transmission, and evolution. *PLoS Pathog.* (2019) 15:e1008089. doi: 10.1371/journal.ppat.1008089
46. Wilder-Smith A, Chiew CJ, Lee VJ. Can we contain the COVID-19 outbreak with the same measures as for SARS? *Lancet Infect Dis.* (2020). doi: 10.1016/S1473-3099(20)30129-8
47. Lin YM, Wang M, Sun NX, Liu YY, Yin TF, Chen C. Screening and application of nutritional support in elderly hospitalized patients of a tertiary care hospital in China. *PLoS ONE.* (2019) 14:e0213076. doi: 10.1371/journal.pone.0213076
48. Bonetti L, Terzoni S, Lusignani M, Negri M, Frolidi M, Destrebecq A. Prevalence of malnutrition among older people in medical and surgical wards in hospital and quality of nutritional care: a multicenter, cross-sectional study. *J Clin Nurs.* (2017) 26:5082–92. doi: 10.1111/jocn.14051
49. Bastoni D, Ticinesi A, Lauretani F, Calamai S, Catalano ML, Catania P, et al. Application of the sepsis-3 consensus criteria in a geriatric acute care unit: a prospective study. *J Clin Med.* (2019) 8:359. doi: 10.3390/jcm8030359
50. Sorbello M, El-Boghdady K, Di Giacinto I, Cataldo R, Esposito C, Falcetta S, et al. The Italian coronavirus disease 2019 outbreak: recommendations from clinical practice. *Anaesthesia.* (2020). doi: 10.1111/anae.15049. [Epub ahead of print].
51. Briguglio M, Hrelia S, Malaguti M, Serpe L, Canaparo R, Dell'Osso B, et al. Food bioactive compounds and their interference in drug pharmacokinetic/pharmacodynamic profiles. *Pharmaceutics.* (2018) 10:277. doi: 10.3390/pharmaceutics10040277

**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2020 Briguglio, Pregliasco, Lombardi, Perazzo and Banfi. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.