Received: 5 July 2021 | Revised: 29 July 2021 | Accepted: 7 August 2021

DOI: 10.1111/pai.13640

SUPPLEMENT ARTICLE

WILEY

Metabolomics, Microbiomics, Machine learning during the COVID-19 pandemic

Flaminia Bardanzellu | **Vassilios Fanos**

Neonatal Intensive Care Unit, Department of Surgical Sciences, AOU University of Cagliari, Cagliari, Italy

Correspondence
Flaminia Bardanzellu, Department of Surgical Sciences, AOU University of Cagliari, Cagliari, Italy.
Email: bardanzellu.flaminia@virgilio.it

Editor: Gian Luigi Marseglia

Abstract

COVID-19 pandemic has a significant impact worldwide, from the point of view of public health, social, and economic aspects. The correct strategies of diagnosis and global management are still under debate. In the next future, we firmly believe that combining the so-called 3 M's (metabolomics, microbiomics, and machine learning [artificial intelligence]) will be the optimal, accurate tool for the early diagnosis of COVID-19 subjects, risk assessment and stratification, patient management, and decision-making. If the currently available preliminary data obtain further confirms, through future studies on larger samples, simple biomarkers will provide predictive models for data analysis and interpretation, allowing a step toward personalized holistic medicine.

KEYWORDS
biomarkers, machine learning, OMICS technologies, SARS-CoV-2, viral spread

1 | INTRODUCTION

COVID-19 pandemic represents a global problem, impairing global health and socioeconomic conditions. To date, there are still doubts and perplexities regarding the currently available diagnostic tools' sensitivity and specificity, time and costs of execution, reagents and trained personnel availability, and the optimal screening time window.[1]In recent years, "omics" technologies affirmed their power in the characterization of several pathophysiological processes. Metabolomics can dynamically detect the whole set of low molecular weight molecules in cells, tissues, organs, and biological fluids, describing individual metabolic responses to drugs, environmental stimuli, lifestyle, diseases, and many epigenetics factors.[2]

Modern medicine moves from a descriptive to an integrated approach that will interpret massive data networks obtained from broad patient cohorts, healthy subjects, and experimental organisms to determine physiologic and pathologic processes specific for each individual.[3] This will mean introducing "artificial intuition," decoding the "black box" of medicine.

We recently investigated "7 secrets" of COVID-19 (fever, ACE2 receptors, gut-lung axis, metabolomics, microbiomics, probiotics, diet) to reveal mechanisms, susceptibility, and weaknesses SARS-CoV-2 infection. In the next future, the combination of the so-called 3 M's (metabolomics, microbiomics, and machine learning [artificial intelligence]), in our opinion, will be the optimal, accurate tool for COVID-19-affected subjects early diagnosis, risk assessment and stratification, patient management, and decision-making.[4]

Metabolomics seems promising to detect specific COVID-19 biomarkers; practically, early diagnosis, individual susceptibility identification, disease and prognosis prediction, drug response assessment, and vaccine eligibility/response could be the future goals of metabolomics application in such a pandemic context. Moreover, metabolomics could help in decoding microbiome variations in the case of SARS-CoV-2 infection.

Some metabolomics studies have been performed in adult patients affected by COVID-19, applying targeted or untargeted methods; changes in lipid homeostasis and several biomarkers have been highlighted, as reviewed in our recent paper.[1] Specific metabolite

resulted in under- or up-regulated in affected patients and appeared helpful to discriminate them from healthy controls.[4]

To date, and from the literature review of the available studies, six simple serum markers and ratio seems the most accurate and could be potentially applied in clinical practice.

In detail, decreased arginine/kynurenine ratio can predict diagnosis with 100% accuracy. Increased kynurenine/tryptophan ratio and decreased glutamine/glutamate ratio can predict disease severity. Decreased Fisher's ratio (valine+leucine+isoleucine)/(phenylalanine+tyrosine) can predict severity too; finally, increased creatinine values and creatinine/arginine ratio can predict mortality in patients admitted to intensive care unit with high accuracy.[5]

Among metabolomics variations, the existing link between *E. coli* and phenylalanine and succinate metabolism plays a central role. Inflammatory pathways of SARS-CoV-2 infection also seem closely related to lipidomic alteration, leading to phospholipids and arachidonic acid variations.

Moreover, some changes in the breast milk of COVID-19 mothers and their possible pathophysiological meaning in the offspring have been reviewed.[6]

In the future, we hypothesize that a targeted approach, through a specific metabolite supplementation, could represent a novel and personalized therapeutic strategy against COVID-19.

Key Messages

OMICS technologies can be applied in the setting of COVID-19 pandemics, improving its management. Specific serum metabolites seem worthwhile in discriminating COVID-19-affected patients from healthy controls. Metabolomics could optimize COVID-19 early diagnosis, individual susceptibility identification, disease and prognosis prediction, drug response assessment, and vaccine eligibility/response. Defining microbial species predisposing to a more invasive SARS-CoV-2 infection could be helpful in the early identification of the most severe COVID-19 cases. Artificial intelligence and Big Data are highly promising in the optimal and personalized treatment of COVID-19

1.1 | Microbiomics

Several differences have been detected by comparing lung and gut **microbiota** of COVID-19-affected patients and healthy controls.[4,7,8]

Lung microbiota can modulate local and systemic effects during SARS-CoV-2 infection, including action on ACE-2 receptors.[7] In some studies, higher broncho-alveolar fluid levels of *Capnocytophaga gingivalis*, *Veillonella spp.*, *Leptotrichia buccalis*, *Veillonella parvula*, and *Prevotella melanogenic* were associated with more severe COVID-19 forms, differently from *Fusobacterium periodonticum*.[4]

Moreover, gut dysbiosis could help define the increased susceptibility to SARS-CoV-2 infection in some patients, including older people, undergoing a reduction in bacterial diversity or subjects affected by comorbidities or inflammatory diseases.

Gut bacteria can interact with intestinal viruses favoring or contrasting their virulence; SARS-CoV-2 can reach the gut. Its invasiveness appeared more pronounced in the case of local dysbiosis, modulating ACE-2 activity and local inflammatory response, and increased gut permeability, potentially leading to hemorrhagic colitis and pneumatosis. In more severe SARS-CoV-2 cases, especially in hospitalized patients, good bacteria are reduced (including Lactobacilli and Bifidobacteria and *F. prausnitzii*), while *Clostridia spp.*, *Actinomyces spp.*, and *Bacteroides spp* are increased.[8] Increased proinflammatory species were detected, including *Klebsiella spp.*, *Streptococcus spp.*, and *R. gnavus*, in addition to increased levels of proinflammatory cytokines, a lower bacterial diversity, and higher disease severity. Some of these modifications overlap with those found in diseases such as diabetes, obesity, irritable bowel disease, and hypertension.[4]

The exact definition of microbial species predisposing to a more invasive SARS-CoV-2 infection could be helpful in the early identification of the most severe COVID-19 cases.

Probiotics, prebiotics, or nanotechnology-related interventions promoting eubiosis could represent therapeutic allies in reducing SARS-CoV-2 virulence and disease severity. Diet and personalized nutrition strategies, adequate vitamin D assumption, physical activity, lifestyle, and reduced use of antibiotics could also be critical points in modulating COVID-19 severity. However, further studies will help clarify the exact interplay among these pathways, even in predisposed patients showing comorbidities.

Artificial intelligence integrates and identifies a specific panel of biomarkers able to contribute to SARS-CoV-2 diagnosis and disease progression monitoring.

This can be achieved through the integration of artificial intelligence–obtained algorithms and "omics" techniques in platforms involving machine learning (ML) to analyze end-to-end mass spectrometry (MS) data.[1]

Big data represent an unprecedented amount of information derived from public health surveillance and real-time epidemic outbreaks monitoring, characterized by rapidity in acquisition and processing, and variety of acquisition source.[9]

Some authors already applied AI and machine learning algorithms in COVID-19 studies, as widely evidenced in the literature survey of Chiroma and colleagues.[10] Recently, Delafiori et al. performed a cross-sectional study on 815 Brazilian individuals, including 442 COVID-19-affected patients, 23 suspected cases, and 350 healthy controls; through the integration of a machine learning-based algorithm with MS on plasma samples analysis, 19 metabolomics discriminating biomarkers were obtained to diagnose COVID-19 infection (specificity >96%, sensitivity >83%) and risk assessment (specificity >80%, sensitivity >85%).[1]

However, although promising in SARS-CoV-2 identification, risk assessment, and management strategies, these are still preliminary data requiring future confirmation.

In a recent paper, the current potential application of AI and Big Data in the COVID-19 pandemic is reviewed. In detail, Bragazzi et al. identify a short-term application (represented by improvement in epidemiological data collection, risk assessment, and public health interventions, as well as the diagnosis anticipation and prognosis evaluation), some medium-term advantages (including the optimization of therapeutic options), and, finally, long-term perspectives (optimizing protocols to face infections and promote global health).[1]

2 | CONCLUSION

It emerges that AI and Big Data are highly promising in the optimal and personalized management of COVID-19 and other acute conditions.

To date, relevant interconnection emerged between COVID-19-related dysbiosis and metabolomics pathways; moreover, probiotics administration could be helpful in the prevention or treatment of severe COVID-19 cases. The integration of such technologies can provide real-time viral spread tracking, orient public health interventions monitoring their efficacy, help discover new drugs and their safety profile; finally, a great potential could be exploited in vaccination campaigns, identifying vaccine efficacy or potential side effects.[9] If the current preliminary data on COVID-19 will be confirmed on larger samples, simple biomarkers could be used to build predictive models for data analysis and interpretation, allowing a step toward personalized holistic medicine.

ACKNOWLEDGEMENTS

Open Access funding provided by Universita degli Studi di Cagliari within the CRUI-CARE Agreement. [Correction added on 11-May-2022, after first online publication: CRUI-CARE funding statement has been added.]

AUTHOR CONTRIBUTIONS

Flaminia Bardanzellu: Conceptualization (equal); Writing-review and editing. **Vassilios Fanos:** Conceptualization (equal); Supervision; Writing-review and editing (equal).

ORCID

Flaminia Bardanzellu https://orcid.org/0000-0001-9889-8047
Vassilios Fanos https://orcid.org/0000-0003-2617-2890

REFERENCES

1. Delafiori J, Navarro LC, Siciliano RF, et al. Covid-19 Automated Diagnosis and Risk Assessment through Metabolomics and Machine Learning. *Anal Chem*. 2021;93:2471-2479.
2. Bardanzellu F, Fanos V. How could metabolomics change pediatric health? *Ital J Pediatr*. 2020;46:37.
3. Hawgood S, Hook-Barnard IG, O'Brien TC, et al. Precision medicine: Beyond the inflection point. *Sci Transl Med*. 2015;7:300.
4. Fanos V, Pintus R, Pintus MC, et al. Seven secrets of COVID-19: fever, ACE2 receptors, gut-lung axis, metabolomics, microbiomics, probiotics, diet. *Journal of Pediatric and Neonatal Individualized Medicine (JPNIM)*. 2021;10:e100145.
5. Mussap M, Fanos V. Could metabolomics drive the fate of COVID-19 pandemic? A narrative review on lights and shadows. *Clinical Chemistry and Laboratory Medicine (CCLM)*. 2021;submitted.
6. Bardanzellu F, Puddu M, Fanos V. Breast Milk, and COVID-19: From Conventional Data to "Omics" Technologies to Investigate Changes Occurring in SARS-CoV-2 Positive Mothers. *Int J Environ Res Public Health*. 2021;18:5668.
7. Fanos V, Pintus MC, Pintus R, et al. Lung microbiota in the acute respiratory disease: from coronavirus to metabolomics. *J Pediatr Neonat Individual Med*. 2020;9:e090139.
8. Marcialis MA, Bardanzellu F, Microbiota FV, Disease C. Microbiota and Coronavirus Disease 2019. Which Came First, the Chicken or the Egg? *Clin Infect Dis* 2021;15;72:2245-2246.
9. Bragazzi NL, Dai H, Damiani G, et al. How Big Data and Artificial Intelligence Can Help Better Manage the COVID-19 Pandemic. *Int J Environ Res Public Health*. 2020;17:3176.
10. Chiroma H, Ezugwu AE, Jauro F, et al. Early survey with bibliometric analysis on machine learning approaches in controlling COVID-19 outbreaks. *PeerJ Comput Sci*. 2020;6:e313.

How to cite this article: Bardanzellu F, Fanos V. Metabolomics, Microbiomics, Machine learning during the COVID-19 pandemic. *Pediatr Allergy Immunol*. 2022; 33(Suppl. 27):86–88. https://doi.org/10.1111/pai.13640