Journal Pre-proof

Effects of Micronutrients or Conditional Amino Acids on COVID-19 Related Outcomes: An Evidence Analysis Center Scoping Review

Mary Rozga, PhD, RDN, Feon W. Cheng, PhD, MPH, RDN, CHTS-CP, Lisa Moloney, MS, RDN, Deepa Handu, PhD, RD, LDN

PII: S2212-2672(20)30515-3

DOI: https://doi.org/10.1016/j.jand.2020.05.015

Reference: JAND 54877

To appear in: *Journal of the Academy of Nutrition and Dietetics*

Received Date: 13 May 2020

Accepted Date: 15 May 2020

Please cite this article as: Rozga M, Cheng FW, Moloney L, Handu D, Effects of Micronutrients or Conditional Amino Acids on COVID-19 Related Outcomes: An Evidence Analysis Center Scoping Review, *Journal of the Academy of Nutrition and Dietetics* (2020), doi: https://doi.org/10.1016/j.jand.2020.05.015.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Copyright © 2020 by the Academy of Nutrition and Dietetics.

Journal Pre-proof

Effects of Micronutrients or Conditional Amino Acids on COVID-19 Related Outcomes: An Evidence Analysis Center Scoping Review

Mary Rozga, PhD, RDN[a*]; Feon W. Cheng, PhD, MPH, RDN, CHTS-CP[b]; Lisa Moloney, MS, RDN[c]; Deepa Handu, PhD, RD, LDN[d]

[a*]Corresponding author.

Keywords: Micronutrients; Conditional Amino Acids; COVID-19; Medical Nutrition Therapy; Nutrition Support

Word Count Abstract: 238

Word Count Manuscript: 2,177

Author Contributions: All authors wrote sections of the first draft, thoroughly edited the manuscript and approved the final draft.

Funding/Financial Disclosures: This work was supported by the Academy of Nutrition and Dietetics.

Conflict of Interest: Authors have no conflicts of interest to disclose.

[a] Nutrition Researcher, Academy of Nutrition and Dietetics Evidence Analysis Center. 120 S. Riverside Plaza, Suite 2190; Chicago, Illinois 60606-6995; ; Phone: 312-899- 1758; email: mrozga@eatright.org

[b] Nutrition Researcher, Academy of Nutrition and Dietetics Evidence Analysis Center. 120 S. Riverside Plaza, Suite 2190; Chicago, Illinois 60606-6995; ; Phone: 312-899- 1757; email: fcheng@eatright.org

[c] Nutrition Researcher, Academy of Nutrition and Dietetics Evidence Analysis Center. 120 S. Riverside Plaza, Suite 2190; Chicago, Illinois 60606-6995; ; Phone: 312-899-4785; email: lmoloney@eatright.org

[d] Senior Scientific Director, Academy of Nutrition and Dietetics Evidence Analysis Center. 120 S. Riverside Plaza, Suite 2190; Chicago, Illinois 60606-6995; Phone: 312-899-4704; email: dhandu@eatright.org

Journal Pre-proof

Effects of Micronutrients or Conditional Amino Acids on COVID-19 Related Outcomes: An Evidence Analysis Center Scoping Review

Abstract

Recent narrative reviews have described the potential efficacy of providing individuals infected with COVID-19 with additional micronutrients to reduce disease severity. While there are compelling reasons why providing additional micronutrients or conditional amino acids may affect COVID-19-related outcomes, evidence is lacking. The objective of this scoping review is to explore and describe the literature examining the effect of providing additional micronutrients or conditional amino acids (glutamine, arginine) in adults with conditions or infections similar to COVID-19 infection on COVID-19 related health outcomes. A literature search of the MEDLINE database and hand-search of Cochrane Database of systematic reviews retrieved 1,423 unique studies, and eight studies were included in this scoping review. Four studies examined a target population with ventilator-related pneumonia and acute respiratory distress syndrome, while the other four studies included patients who were at risk for ventilator-associated pneumonia. Interventions included intravenous vitamin C, intramuscular vitamin D, enteral and intramuscular vitamin E, enteral zinc sulfate, and oral and parenteral glutamine. In six of the eight included studies, baseline status of the nutrient of interest was not reported and, thus, it is uncertain how outcomes may vary in the context of nutrient deficiency or insufficiency compared to sufficiency. In the absence of direct evidence examining efficacy of providing additional micronutrients or conditional amino acids to standard care, registered dietitian nutritionists (RDNs) must rely on clinical expertise, and indirect evidence to guide medical nutrition therapy (MNT) for patients infected with COVID-19.

Introduction

The COVID-19 pandemic has resulted in immeasurable adverse health effects across the world. Recent narrative reviews have described the potential efficacy of providing additional micronutrients to reduce disease severity in individuals infected with COVID-19.[1-3] Suspected efficacy of providing additional micronutrients to patients in order to reduce disease severity is based on known mechanisms of micronutrients, including in optimizing the immune system and reducing inflammation, as well as results from trials with humans infected with other viruses and in animal models of coronavirus. These narratives describe compelling reasons why providing micronutrients, particularly vitamins C and D, may treat underlying insufficiencies or deficiencies to benefit immune function prior to and after contracting COVID-19 infection.

In addition to optimizing immune function, another key consideration when providing medical nutrition therapy (MNT) to critically ill patients infected with the COVID-19 virus is the increased risk for malnutrition. Nutrition support is in high demand for critically ill patients being treated in Intensive Care Units (ICUs) during the current pandemic.[4-6] While conditional amino acids are not essential in healthy individuals, needs are increased during critical illness, and these amino acids become essential. While nutrition support provides essential nutrients, it is possible that providing conditional amino acids, which become essential in the context of critical care, above those provided in standard nutrition support may allow for increased capacity for recovery and maintenance or improvement of nutritional status.[7] However, evidence is lacking regarding the effect of providing additional conditional amino acids in the context of critical illness due to COVID-19 infection.

In order to provide evidence-based practice, it is important to determine the evidence available to support nutrition interventions. In the absence of direct evidence to support nutrition interventions for the population of interest, practitioners must depend upon their clinical expertise and indirect evidence. While there is ample evidence to suggest that supplementing or fortifying nutrition support with micronutrients or conditional amino acids may be beneficial for COVID-19 patients, there is little evidence directly testing these interventions in this population. Therefore, the objective of this scoping review is to explore and describe the literature examining the effect of providing additional micronutrients or conditional amino acids (glutamine, arginine) on COVID-19-related health outcomes in adults with conditions or infections similar to COVID-19 infection.

Methods

This scoping review followed the protocols developed by Arskey and O'Malley[8] and refined by Levac[9] et al and the Joanna Briggs Institute.[10] The protocol for this scoping review adheres to the PRISMA scoping review checklist[11] and was registered on Open Science Framework (https://osf.io/9rm6u/).[12]

Eligibility Criteria

This scoping review defined the research question and eligibility criteria according to the Population-Concept-Context approach.[10] The populations of interest were humans infected with a type of coronavirus (COVID-19, SARS, MERS), with ARDS, or those at-risk-of or with ventilator-associated pneumonia, since findings in these populations may inform individuals

Journal Pre-proof

currently infected with the COVID-19 coronavirus. The concept of this scoping review is provision of additional micronutrients or the conditional amino acids glutamine or arginine. The context was left open to capture all potential articles examining populations of interest. There were no limits on publication dates. Only articles published in English were included in this scoping review due to resource constraints. Additional eligibility criteria can be found in **Table 1**.

Search Plan

MEDLINE (EBSCO) database was searched on April 21, 2020 to identify titles and abstracts with both the population and concept of interest. Search terms for the coronavirus were adapted from a recent search strategy developed by the National Institute for Health and Care Excellence for this project.[13] Additional search terms included "micronutrient", "ascorbic acid", "vitamin D", "zinc", "multivitamin", "glutamine" and "arginine". The only filter used was for the English language. A detailed search plan can be found in **Appendix 1**. Relevant systematic and narrative reviews as well as the Cochrane Database of Systematic Reviews were hand-searched for potentially included studies not identified in the MEDLINE search.

Study Selection and Data Extraction

Title and abstract screening were conducted in two phases using Rayyan, an online software program.[14] In the first phase, a reviewer (M.R.) excluded studies with animals or cells as the population of interest as well as studies that were not primary research studies or systematic reviews. Any remaining abstracts were reviewed by two independent reviewers. Full-texts of

Journal Pre-proof

potentially included articles were reviewed for eligibility by two reviewers (M.R. and F.W.C.), and discrepancies were settled through consensus. Each stage of the review process was documented in a PRISMA flow chart.[15]

Data were extracted from included studies, including: bibliographic information; details on the target population including disease/illness status, ventilator status and age; details on the intervention including the nutrient, dose, mode and duration; outcomes of interest reported and summary of study results. This data was extracted onto a standardized study characteristics table. Studies with similar populations and/or interventions were grouped and described narratively. As is customary for scoping reviews, no critical appraisal of study quality was conducted.

Results

There were 1,423 unique studies identified with the database search, full-texts of eleven studies were examined for inclusion, and eight studies were included in this scoping review (**Figure 1**).[16-24] The majority of the studies identified in the initial search were excluded during title/abstract screening. Primary reasons for exclusion were: animals or cell studies; human studies did not examine a population of interest, and; studies were not primary research studies (e.g., narrative reviews and commentaries).

Characteristics of the eight included studies are shown in **Table 2**. There were five randomized controlled trials represented in six publications[16,17,19,21-23] and three non-randomized controlled studies,[18,20,24] published between 1987[20] and 2019.[16] The number of participants ranged from 14[20] to 186.[24] Although all studies included critically ill patients, the sample characteristics

differed slightly. For example, Lin et al included patients in burn shock resuscitation,[18] while Kaya et al included ventilated patients in neurosurgical ICU.[17]

Four studies focused on patients who had ventilator-related pneumonia and/or acute respiratory distress syndrome,[16,19,20,23] and the remaining four studies included patients who were at risk for ventilator-associated pneumonia.[17,18,22,24]

Study interventions were heterogeneous. Fowler et al[16] and Lin et al[18] examined the effect of vitamin C or ascorbic acid via intravenous infusion and the remaining included studies investigated other single nutrients delivered through various modes: glutamine orally[17] or parenterally[22]; vitamin D intramuscularly[19]; vitamin E (d,1-alpha-tocopherylacertate) enterally[20] or intramuscularly[23]; and zinc sulfate enterally.[24] The duration of the intervention also varied (**Table 2**).

Except for Lin et al[18] and Seeger et al,[20] all other six studies had a comparison group.[16,17,19,22-24] Among the eight included studies, reported outcomes included: organ failure, inflammatory and vascular injury markers, pneumonia score, ventilator-related pneumonia, and mortality.

Five studies did not find any improvement in their reported outcomes.[16-18,20,22] In three studies the authors reported a potential benefit of the intervention on outcomes: intramuscular vitamin D on mortality,[19] intramuscular vitamin E on Acute Physiology and Chronic Health Evaluation (APACHE) score in patients with ARDS,[23] and zinc sulfate on the incidence of ventilator-associated pneumonia in ventilated ICU patients.[24] In two studies, authors indicated deficiency of the nutrient of interest at baseline,[16,19] but baseline status of the intervention nutrient was not described in the remaining studies.

Journal Pre-proof

Journal Pre-proof

Discussion

This scoping review included eight unique studies examining the effect of providing additional micronutrients or conditional amino acids on COVID-19-related health outcomes in individuals with ARDS and in individuals with or at risk for ventilator-associated pneumonia. Although the search plan included individuals infected with a form of coronavirus (COVID-19, SARS, MERS), there were no studies identified with these target populations. Overall, sparse evidence of heterogeneous interventions described some benefit of intramuscular vitamins D and E, and zinc via a nasogastric tube on coronavirus-related outcomes, but findings should be interpreted with caution since this scoping review did not critically analyze risk of bias or certainty of evidence. In addition, most studies did not report the baseline status of the nutrients being supplemented. Thus, it is unclear if results would have been different if participants were exclusively insufficient/deficient vs sufficient. It is possible that treating baseline deficiency may result in improved outcomes,[25] while providing additional nutrients to a sufficient individual would result in no effect. Hence, further investigation is warranted.

There has been considerable interest in the efficacy of micronutrient therapy to reduce the severity and symptoms of COVID-19 infection, particularly in the context of critical illness.[1-3,26,27] Recent reviews include comprehensive discussion of the potential effects of providing additional micronutrients to individuals with COVID-19,[1] particularly vitamin C[3,28] and vitamin D[2,26,27]. In these reviews, the authors provide compelling logic that patients infected with COVID-19 or with comparable conditions could benefit from addition of these nutrients. Authors describe biological functions of these micronutrients and discuss how supplementation has been effective in treating other viruses such as the common cold or influenza, particularly in the context of insufficiency or deficiency. Authors also provide evidence describing efficacy of

providing micronutrients in the context of animal models of coronavirus. However, human trials examining efficacy of providing micronutrients and conditional amino acids were lacking, which was supported by the dearth of evidence discovered in this scoping review.

There is minimal available evidence to guide nutrition care for RDNs working with patients infected with COVID-19. Indeed, there is little evidence to guide practice for individuals with similar conditions, including alternative versions of the coronavirus, ARDS or ventilator-associated pneumonia. In these circumstances, it is critical for RDNs to rely on their scientific training, clinical expertise, and the nutrition care process to determine if a patient is deficient in an essential nutrient and if treating the respective deficiency is a priority. RDNs can also extrapolate evidence from populations presenting with similar signs and symptoms, such as those with critical illness and/or on mechanical ventilation, to inform practice for individuals with COVID-19 infections. RDNs should consider how baseline nutrient status may affect outcomes, since treating a deficiency or insufficiency may result in improved outcomes, while providing nutrients above meeting needs may have no effect.

In the current COVID-19 crisis, it is not possible to wait until clinical trials are published on each intervention delivered before implementing the intervention with a patient, as would ideally be the case in standard care. Instead, RDNs must use ingenuity and innovation and work as part of a multi-disciplinary team to determine priorities and risk-benefit ratio of interventions when collaborating to manage health condition in adults infected with COVID-19.

COVID-19 Research Moving Forward

In a recent consensus report, the Expert Group on Clinical Treatment of New Corona Virus Disease in Shanghai described that high-dose intravenous vitamin C treatment is recommended for patients with light or general symptoms[29] to prevent and control cytokine storms. Several trials have been registered examining the effect of providing antioxidants,[30] vitamin C,[31-35] and vitamin D.[36-38] Thus, while there is no research to support evidence-based recommendations at this time, evidence to inform provision of additional micronutrients for individuals with COVID-19 infections may be available moving forward. There were no registered trials found directly examining the effects of glutamine or arginine.

In order to provide evidence-based practice for RDNs, it is crucial that RDNs participate in COVID-19 related research when possible. In addition to participating in formal research studies, RDNs can contribute their experiences in delivering MNT to this population by documenting care and outcomes in the Academy of Nutrition and Dietetics Health Informatics Infrastructure (ANDHII).[39] RDNs working with COVID-19 patients are essential workers and are likely stressed for time. However, any documentation of current practices can help contribute to a growing pool of evidence supporting the efficacy of MNT in COVID-19 affected patients.

Strengths and Limitations

This scoping review followed a rigorous process and examined the availability of interventions of potential utility in populations that may be comparable and applicable to the COVID-19 infected population. A limitation of this scoping review included the lack of evidence available in target populations and lack of documentation of baseline nutrient status of participants in included articles. Moving forward, authors of scoping and systematic reviews examining

Journal Pre-proof

potential efficacy of interventions in patients with COVID-19 infection should consider including a broader population base, including those with critical illness or respiratory infections, in order to identify evidence that can be extrapolated to the population of interest. Another limitation of this scoping review was searching the MEDLINE database and Cochrane Database of Systematic Reviews only in the interest of providing information to practitioners in a rapid manner. However, studies cited in the included articles or in any relevant narrative reviews were evaluated for inclusion. This scoping review did not cover all nutrients that may be beneficial to COVID-19 patients, including probiotics or oral nutrition supplements.

Conclusion

Individuals infected with COVID-19 may have baseline nutrient deficiencies and/or increased nutrient needs due to COVID-19 pathology. Current reviews and registered trials discuss the potential utility of providing additional micronutrients and glutamine in contexts that may apply to those infected with COVID-19. However, evidence in human subjects is very limited and it is unclear if results may vary according to baseline nutrient status. RDNs must work with the multidisciplinary team and rely on clinical expertise and indirect evidence to guide MNT for patients infected with COVID-19 in order to reduce adverse effects from COVID-19 infection.

Journal Pre-proof

Journal Pre-proof

References

1. Zhang L, Liu Y. Potential interventions for novel coronavirus in China: A systematic review. *J Med Virol.* 2020;92(5):479-490.
2. Grant WB, Lahore H, McDonnell SL, et al. Evidence that Vitamin D Supplementation Could Reduce Risk of Influenza and COVID-19 Infections and Deaths. *Nutrients.* 2020;12(4).
3. Cheng RZ. Can early and high intravenous dose of vitamin C prevent and treat coronavirus disease 2019 (COVID-19)? *Med Drug Discov.* 2020;5:100028.
4. Laviano A, Koverech A, Zanetti M. Nutrition support in the time of SARS-CoV-2 (COVID-19). *Nutrition.* 2020:110834.
5. Martindale R PJ, Taylor B, Warren M, McClave S. Nutrition Therapy in the Patient with COVID-19 Disease Requiring ICU Care. American Society for Parenteral and Enteral Nutrition, Society of Critical Care Medicine. Available at: https://www.sccm.org/getattachment/Disaster/Nutrition-Therapy-COVID-19-SCCM-ASPEN.pdf?lang=en-US. Accessed: April 1, 2020 2020.
6. Iyer R, Bansal A. What do we know about optimal nutritional strategies in children with pediatric acute respiratory distress syndrome? *Ann Transl Med.* 2019;7(19):510.
7. Morris CR, Hamilton-Reeves J, Martindale RG, Sarav M, Ochoa Gautier JB. Acquired Amino Acid Deficiencies: A Focus on Arginine and Glutamine. *Nutr Clin Pract.* 2017;32(1_suppl):30s-47s.
8. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. *Int J Soc. Res Methodol: Theory & Prac.* 2005: 8(1):19-32.

Journal Pre-proof

9. Levac D, Colquhoun H, O'Brien KK. Scoping studies: advancing the methodology. *Implement Sci.* 2010;5:69.

10. Peters MDJ GCMP, Baldini Soares C, Khalil H, Parker D. Chapter 11: Scoping Reviews (2020 version). In: *Joanna Briggs Institute Reviewer's Manual, JBI, 2020.* .2017.

11. Tricco AC, Lillie E, Zarin W, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. *Ann Intern Med.* 2018;169(7):467-473.

12. Rozga M. The Effect of Micronutrient and Single Amino Acid Supplementation on Coronavirus-related Outcomes: A Scoping Review. Open Science Framework. osf.io/9rm6u. Published 2020. Accessed April 24, 2020.

13. The National Institute for Health and Care Excellence (NICE). Interim process and methods for developing rapid guidelines on COVID-19, 7 Appendix: search strategy for Medline (Ovid Platform). https://www.nice.org.uk/process/pmg35/chapter/appendix-search-strategy-for-medline-ovid-platform. Published 2020. Accessed April 25, 2020.

14. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. *Syst Rev.* 2016;5(1):210.

15. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol.* 2009;62(10):1006-1012.

16. Fowler AA, 3rd, Truwit JD, Hite RD, et al. Effect of Vitamin C Infusion on Organ Failure and Biomarkers of Inflammation and Vascular Injury in Patients With Sepsis and Severe Acute Respiratory Failure: The CITRIS-ALI Randomized Clinical Trial. *JAMA.* 2019;322(13):1261-1270.

Journal Pre-proof

17. Kaya H, Turan Y, Tunalı Y, et al. Effects of oral care with glutamine in preventing ventilator-associated pneumonia in neurosurgical intensive care unit patients. *Appl Nurse Res.* 2017;33:10-14.

18. Lin J, Falwell S, Greenhalgh D, Palmieri T, Sen S. High-Dose Ascorbic Acid for Burn Shock Resuscitation May Not Improve Outcomes. *Burn Care Res.* 2018;39(5):708-712.

19. Miroliaee AE, Salamzadeh J, Shokouhi S, Sahraei Z. The study of vitamin D administration effect on CRP and Interleukin-6 as prognostic biomarkers of ventilator associated pneumonia. *J Crit Care.* 2018;44:300-305.

20. Seeger W, Ziegler A, Wolf HR. Serum alpha-tocopherol levels after high-dose enteral vitamin E administration in patients with acute respiratory failure. *Intensive Care Med.* 1987;13(6):395-400.

21. Miroliaee AE, Salamzadeh J, Shokouhi S, et al. Effect of Vitamin D Supplementation on Procalcitonin as Prognostic Biomarker in Patients with Ventilator Associated Pneumonia Complicated with Vitamin D Deficiency. *Iran J Pharm Res.* 2017;16(3):1254-1263.

22. Aydogmus MT, Tomak Y, Tekin M, Kati I, Huseyinoglu U. Glutamine supplemented parenteral nutrition to prevent ventilator-associated pneumonia in the intensive care unit. *Balkan Med J.* 2012;29(4):414-418.

23. Hajimahmoodi M, Mojtahedzadeh M, GhaffarNatanzi N, et al. Effects of vitamin E administration on APACHE II Score in ARDS patients. *DARU:J of Pharmaceutical Sci.* 2009: 17(1):24-28.

24. Hasanzadeh Kiabi F, Alipour A, Darvishi-Khezri H, Aliasgharian A, Emami Zeydi A. Zinc Supplementation in Adult Mechanically Ventilated Trauma Patients is Associated

Journal Pre-proof

with Decreased Occurrence of Ventilator-associated Pneumonia: A Secondary Analysis of a Prospective, Observational Study. *Indian J Crit Care Med.* 2017;21(1):34-39.

25. Marik PE, Kory P, Varon J. Does vitamin D status impact mortality from SARS-CoV-2 infection? *Med Drug Discov.* 2020:100041.

26. Weng H, Li J-G, Mao Z, Zeng X-T. Randomised trials of vitamin D 3 for critically ill patients in adults: systematic review and meta-analysis with trial sequential analysis. *Intensive Care Med.* 2017;43(2):277-278.

27. Molloy EJ, Murphy N. Vitamin D, Covid-19 and Children. *Ir Med J.* 2020;113(4):64.

28. Boretti A, Banik BK. Intravenous Vitamin C for reduction of cytokines storm in Acute Respiratory Distress Syndrome. *PharmaNutrition.* 2020:100190.

29. Shanghai Expert Group on Clinical Treatment of New Coronavirus Diseases. Expert Consensus on Comprehensive Treatment of Cornoavirus Diseases in Shanghai in .2019 comprehensive treatment of coronavirus disease expert consensus *China Journal of Infectious Diseases.* 2020:38. DOI:10.3760/cma.j.issn.1000-6680.2020.0016.

30. ClinicalTrials.gov [Internet]. Anti-inflammatory/Antioxidant Oral Nutrition Supplementation in COVID-19 (ONSCOVID19); NCT04323228. National Library of Medicine (US). https://clinicaltrials.gov/ct2/show/NCT04323228. Published 2020. Accessed April 28, 2020.

31. ClinicalTrials.gov [Internet]. Early Infusion of Vitamin C for Treatment of Novel COVID-19 Acute Lung Injury (EVICT-CORONA-ALI); NCT04344184. National Library of Medicine (US). https://clinicaltrials.gov/ct2/show/NCT04344184. Published 2020. Accessed April 28, 2020.

Journal Pre-proof

32. ClinicalTrials.gov [Internet]. Administration of Intravenous Vitamin C in Novel Coronavirus Infection (COVID-19) and Decreased Oxygenation (AVoCaDO); NCT04357782. National Library of Medicine (US). https://clinicaltrials.gov/ct2/show/NCT04357782. Published 2020. Accessed April 28, 2020.

33. ClinicalTrials.gov [Internet]. Pharmacologic Ascorbic Acid as an Activator of Lymphocyte Signaling for COVID-19 Treatment; NCT04363216. National Library of Medicine (US). https://clinicaltrials.gov/ct2/show/NCT04363216. Published 2020. Accessed April 28, 2020.

34. ClinicalTrials.gov [Internet]. Use of Ascorbic Acid in Patients With COVID 19; NCT04323514. National Library of Medicine (US). https://clinicaltrials.gov/ct2/show/NCT04323514. Published 2020. Accessed April 28, 2020.

35. ClinicalTrials.gov [Internet]. Vitamin C Infusion for the Treatment of Severe 2019-nCoV Infected Pneumonia; NCT04264533. National Library of Medicine (US). https://clinicaltrials.gov/ct2/show/NCT04264533. Published 2020. Accessed April 28, 2020.

36. ClinicalTrials.gov [Internet]. Vitamin D on Prevention and Treatment of COVID-19 (COVITD-19); NCT04334005. National Library of Medicine (US). https://clinicaltrials.gov/ct2/show/NCT04334005. Published 2020. Accessed April 28, 2020.

37. ClinicalTrials.gov [Internet]. Impact of Zinc and Vitamin D3 Supplementation on the Survival of Aged Patients Infected With COVID-19 (ZnD3-CoVici); NCT04351490.

Journal Pre-proof

National Library of Medicine (US). https://clinicaltrials.gov/ct2/show/NCT04351490. Published 2020. Accessed April 28, 2020.

38. ClinicalTrials.gov [Internet]. COvid-19 and Vitamin D Supplementation: a Multicenter Randomized Controlled Trial of High Dose Versus Standard Dose Vitamin D3 in High-risk COVID-19 Patients (CoVitTrial); NCT04344041. National Library of Medicine (US). https://clinicaltrials.gov/ct2/show/NCT04344041. Published 2020. Accessed April 28, 2020.

39. Academy of Nutrition and Dietetics. ANDHII. Academy of Nutrition and Dietetics. https://www.eatrightpro.org/research/projects-tools-and-initiatives/andhii. Accessed 2020, April 28.

Journal Pre-proof

Journal Pre-proof

Table 1. Eligibility Criteria for a Scoping Review Examining the Effect of Providing Micronutrients or Conditional Amino Acids in COVID-19-Related Conditions on COVID-19-Related Outcomes

Category	**Inclusion Criteria**	**Exclusion Criteria**
Study Type	Peer-reviewed literature	Grey literature
Population	Individuals with suspected or confirmed viral infections related to the coronavirus (COVID-19, SARS, MERS) or acute respiratory disease (ARDS) or who are at-risk-for or with ventilator-associated pneumonia Human	Individuals with no suspected or confirmed viral infections related to the coronavirus (COVID-19, SARS, MERS) or acute respiratory disease (ARDS) or who are not at-risk-for or with ventilator-associated pneumonia Newborn/preterm human infants Animal studies; cell/in vitro studies
Intervention	Vitamins and mineral supplements, including vitamins A, B, C, D, E, zinc, colloidal silver, Multivitamin Single amino acids: glutamine, arginine	Does not examine the effect of specified nutrient Herbal supplements
Comparison	No limits	No limits
Outcomes	Mortality Quality of Life (QoL) Development of COVID-19 or	Outcomes that are not Coronavirus- or Nutrition-Related

Journal Pre-proof

	ventilator-associated pneumonia Hospital Admission Intubation Days on Ventilator Length of stay (LOS) Symptom severity Nutrition/BMI Status Other Coronavirus- and Nutrition-Related Outcomes	
Setting	No limits	No limits
Sample Size	No limits	No limits
Study Designs	Intervention and observational primary studies Systematic review and meta-analyses	Narrative reviews, commentary, editorials, letters to the editor, conference abstracts
Year Range	No limits	No limits
Language	English	Non-English

Journal Pre-proof

Table 2. Study Characteristics and Major Results for Studies Included in a Scoping Review Examining Efficacy of Providing Additional Micronutrients or Conditional Amino Acids on Coronavirus-Related Outcomes

Study	**Population**	**Intervention**	**Comparison Group**	**Outcomes Reported**	**Major Results**
Vitamin C					
Fowler et al 2019[14] RCT PMID 31573637	N = 167 ICU patients with sepsis and acute respiratory distress syndrome Plasma ascorbate levels at baseline were marginally deficient in both groups Mean ±SD Age: 54.8 ± 16.7	Nutrient: **Vitamin C** Dose: 50mg/kg in dextrose 5% in water Mode: Intravenous infusion Duration: Every 6 hours for 96 hours	Placebo (dextrose 5% in water only)	Organ failure (modified Sequential Organ Failure Assessment score), C-reactive protein levels, thrombomodulin levels	Compared to placebo, vitamin C did not significantly improve reported outcomes.
Lin et al 2018[16] Retrospective case-control PMID 29931212	N=80 Patients in burn shock resuscitation Baseline vitamin C status not reported Mean ±SD Age: 41±15 (intervention group) and 42.4±17	Nutrient: high dose **ascorbic acid** Dose: started at a dose of 66 mg/kg/hr Mode: Intravenous infusion Duration: mean time 4:01 ± 15	No treatment	Ventilator-associated pneumonia, mortality	There were no significant differences in the incidence of ventilator-associated pneumonia or mortality between the two groups.

Journal Pre-proof

	(comparison group)	hours			
Vitamin D					
Miroliaee et al 2017[19], 2018[17] RCT PMID 29248753 29201115	N=49 Patients with Ventilator-related pneumonia and vitamin D deficiency Mean ±SD Age: 57.83±18.84 (intervention group) and 56.45±20.70 (comparison group)	Nutrient: **Vitamin D** Dose: 300,000 Units Mode: intramuscular Duration: N/A	Placebo	IL-6, CRP, CPIS score (pneumonia score), sequential organ failure assessment (SOFA) score, mortality	Compared to placebo, vitamin D group had significantly lower IL-6 levels and mortality, but not CRP level and SOFA or CPIS score.
Vitamin E					
Hajimahmoodi et al 2009[21] RCT No PMID	N = 20 ICU patients with acute respiratory distress syndrome Vitamin E status at baseline was not reported Mean ±SD Age: 51.2 ± 6.41	Nutrient: **Vitamin E** (600 IU/day) Mode: Intramuscular Duration: 3 days	Placebo (normal saline)	Acute Physiology and Chronic Health Evaluation (APACHE) II score	Vitamin E appeared to be beneficial in decreasing APACHE II score (significant changes in APACHE II in the intervention group).

Journal Pre-proof

Seeger et al 1987[18] Before-after Study PMID 3117857	N=14 Ventilated and intubated Acute Respiratory Failure patients in ICU Vitamin E status at baseline was not reported Participant ages not reported	Nutrient: **Vitamin E** (d,1-alpha-tocopherylacertate) Dose: 3 gram/day Mode: Enteral (liquid oil directly in gastric tube in 6 doses) Duration: 10 days or if mechanical ventilation is not needed before 10 days	No comparison group	Mortality	No difference in mortality according to the increase in plasma tocopherols from the intervention
Zinc					
Hasanzadeh et al 2017[22] Prospective Cohort Study PMID 28197049	N= 186 Adult mechanically ventilated trauma patients in the ICU Zinc status at baseline was not reported Zinc 24.4% <30 years	Nutrient: **Zinc sulfate** Dosage: 60-90mg/day Mode: Nasogastric tube Duration: 1 year	No zinc sulfate	Occurrence of ventilator-associated pneumonia measured with Clinical Pulmonary Infection Score	Patients receiving zinc sulfate had a smaller hazard of progression to ventilator associated pneumonia

Journal Pre-proof

	51.2% 30-65 years 24.4% >65 years No zinc 21.2% < 30 years 50% 30-65 years 28.8% >65 years				
Glutamine					
Aydoğmuş et al 2012[20] RCT PMID 25207045	N=40 in glutamine and comparison groups Patients on mechanical ventilator support for at least 7 days in the ICU Mean ±SD Age: Non- Glutamine group: 45 ±18.2 years Glutamine group: 36.35 ±16.37 years	Nutrient: **Glutamine** Dose: 40 g/day Mode: TPN Duration: 7 days	TPN without glutamine	Development of ventilator-associated pneumonia, CRP	There was no difference development of ventilator associated pneumonia or CRP levels between groups.
Kaya et al 2016[15]	N=88	Nutrient:	Oral care with 2% chlorhexidine	Ventilator-related pneumonia	No difference between groups at

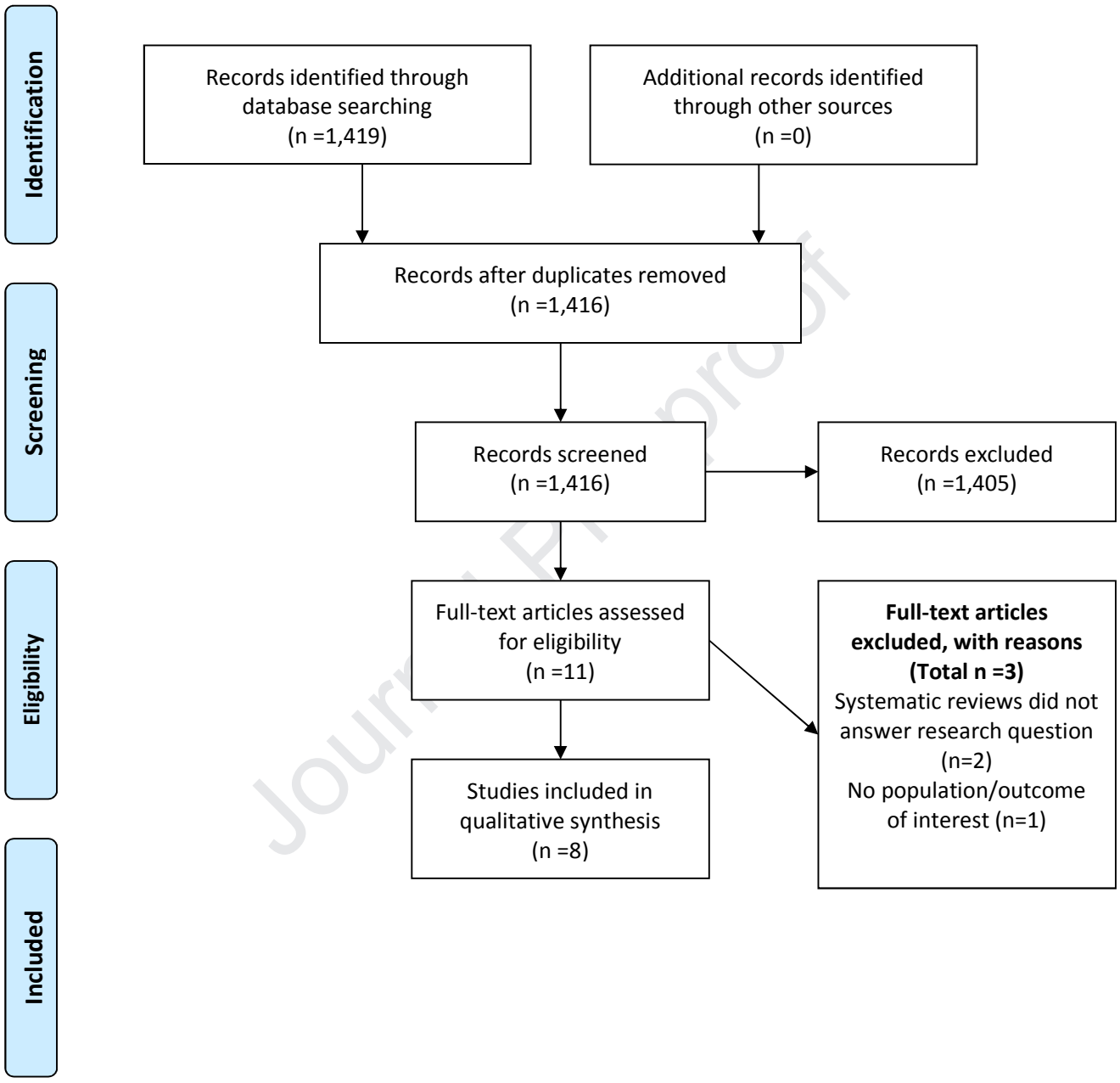
Journal Pre-proof

RCT PMID 28096000	Ventilated patients in neurosurgical ICU; expected to be ventilated at least 5 days Mean ±SD Age: 48.57±17.36	**Glutamine** Concentration: 5% Mode: Oral care Duration: 5 days	gluconate solution	measured with Clinical Infection Score (chest x-rays; endotracheal aspirate cultures), Acute APACHE II score	day 1, 3 or 5 ($p>0.05$)

APACHE= Acute Physiology and Chronic Health Evaluation ; CPIS= Clinical Pulmonary Infection Score; CRP= C-Reactive Protein; ICU= Intensive Care Unit; IL-6= Interleukin 6; RCT= Randomized Controlled Trial; SD= Standard Deviation; TPN= total parenteral nutrition

Journal Pre-proof

Figure 1. PRISMA Flow Diagram for Scoping Review Examining the Effect of Micronutrients and Conditional Amino Acids in COVID-19-Related Conditions on COVID-19-Related Outcomes



Journal Pre-proof

Journal Pre-proof

Appendix 1. MEDLINE search plan for scoping review examining efficacy of providing additional micronutrients and conditional amino acids on COVID-19 related outcomes

Date Searched: April 21, 2020

Limits: English language

#	**Query**
S21	S10 AND S20
S20	S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19
S19	(MH "Glutamine+") OR (MH "Alanine+") OR (MH "Arginine+")
S18	colloidal silver
S17	(MH "Zinc+")
S16	(MH "Vitamin E+")
S15	(MH "Vitamin D+")
S14	(MH "Ascorbic Acid+")
S13	(MH "Vitamin B 12+") OR (MH "Vitamin B 6+") OR (MH "Thiamine+") OR (MH "Vitamin B Complex")
S12	(MH "Vitamin A+") OR (MH "beta Carotene")
S11	(MH "Micronutrients+")
S10	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9
S9	(MH "Respiratory Distress Syndrome, Adult")
S8	(MH "Pneumonia, Ventilator-Associated")
S7	(MH "Middle East Respiratory Syndrome Coronavirus")
S6	(MH "Severe Acute Respiratory Syndrome") OR (MH "SARS Virus")

Journal Pre-proof

S5	((outbreak* or wildlife* or pandemic* or epidemic*) adj1 (China* or Chinese* or Huanan*))
S4	(((respiratory* adj2 (symptom* or disease* or illness* or condition*)) or "seafood market*" or "food market*") adj10 (Wuhan* or Hubei* or China* or Chinese* or Huanan*))
S3	((corona* or corono*) adj1 (virus* or viral* or virinae*))
S2	(coronavirus* or coronovirus* or coronavirinae* or Coronavirus* or Coronovirus* or Wuhan* or Hubei* or Huanan or "2019-nCoV" or 2019nCoV or nCoV2019 or "nCoV-2019" or "COVID-19" or COVID19 or "CORVID-19" or CORVID19 or "WN-CoV" or WNCoV or "HCoV-19" or HCoV19 or CoV or "2019 novel*" or Ncov or "n-cov" or "SARS-CoV-2" or "SARSCoV-2" or "SARSCoV2" or "SARS-CoV2" or SARSCov19 or "SARS-Cov19" or "SARSCov-19" or "SARS-Cov-19" or Ncovor or Ncorona* or Ncorono* or NcovWuhan* or NcovHubei* or NcovChina* or NcovChinese*)
S1	(MH "Coronavirus Infections+") OR (MH "Coronavirus+")

Journal Pre-proof