Association Between SARS-CoV-2 RNAemia and Post-Acute Sequelae of COVID-19.

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Funding

This work was supported by NIH/NIAID (Grants R01AI153133, R01AI137272, and 3U19AI057229 – 17W1 COVID SUPP #2) and a donation from Eva Grove.

Abstract

Determinants of Post-Acute Sequelae of COVID-19 are not known. Here we show that 75% of patients with viral RNA in blood (RNAemia) at presentation were symptomatic in the post-acute phase. RNAemia at presentation successfully predicted PASC, independent of patient demographics, initial disease severity, and length of symptoms.

Keywords

SARS-CoV-2, RNAemia, PASC, long COVID

Background

The determinants of COVID-19 severity and extrapulmonary complications have now been well studied, and RNAemia (viral RNA in blood) has emerged as an important factor (1,2). Much less is known about the determinants of Post-Acute Sequelae of COVID-19 (PASC), the persistence or development of new symptoms after the acute phase of infection, recently reported to affect as many as 87.4% of COVID-19 patients (3,4) primarily with moderate or worse severity (5,6). Recent evidence suggested persistent clotting protein pathology with elevated levels of antiplasmin (7) and non-classical monocytes (8) in patients with PASC. Discovery of SARS-CoV-2 S1 protein in these non-classical monocytes and fragmented SARS-CoV-2 RNA in peripheral blood mononuclear cells in a PASC patient 15 months post infection further exhibited the persistence of viral particles (8). Given the importance of RNAemia in disease severity and its persistence in the blood, we describe the relationship between RNAemia at presentation and post-acute symptoms at least three weeks after symptom onset.

Methods

We studied the clinical trajectories of 155 patients enrolled in the IRB-approved (eP-55650) Stanford Hospital Emergency Department (ED) COVID-19 Biobank between April and November 2020 with completed follow-ups. We assessed symptoms and severity (based on a modified WHO scale) (1) on the date of enrollment (median = 4, range = 0 – 44 days after symptom onset), and at least three weeks after symptom onset (median = 35, range = 21 – 79 days).

We measured SARS-CoV-2 RNAemia at the time of enrollment, using the definitions of our earlier study (1). We compared the proportions of initially RNAemic and non-RNAemic patients with persistent or new symptoms in the post-acute phase using a 2-sample chi-squared test with continuity correction. We estimated the association between RNAemia at enrollment and PASC at follow-up in a logistic model controlling for disease severity at enrollment, patient demographics (age and gender), presence of any symptom at enrollment (anxiety, dizziness, fatigue, hair loss, palpitations, rash, insomnia, chest pain, chills, cough, decrease in sense of taste, fever, nausea/vomiting/diarrhea, headache, loss of smell, myalgia, new confusion, shortness of breath), and durations of symptoms. We also compared the median number of PASC symptoms for RNAemic and non-RNAemic patients using the Wilcoxon rank-sum test with continuity correction. We performed all analyses in R (version 4.0.3).

Results

49.0% (76/155) of patients were women, and the median age was 45 years (IQR 34 – 60). At enrollment, 27.1% (42/155) of patients had mild disease severity, 67.7% (105/155) moderate, and 5.2% (8/155) severe. Patients had a median of six symptoms (IQR = 4–8): 72.3% (112/155) had a cough, 65.3% (101/155) had shortness of breath, and 64.5% (99/155) had fever. In the post-acute phase, 52.3% (81/155) had one or more new (24.5% [38/155]) or persistent (37.4% [58/155]) symptoms, of which the most common were cough, dizziness, and loss of smell (Table 1). 1.3% (2/155) of patients developed anxiety that was not present at enrollment.

75.0% (27/36) of initially RNAemic patients were symptomatic in the post-acute phase, compared to 43.7% (52/119) of non-RNAemic patients (difference = 31.3% [95% CI, 12.8% - 49.8%], p=0.002). RNAemic patients had a median of one symptom in the post-acute phase compared to zero in non-RNAemic patients (p=0.014, Wilcoxon rank-sum test). RNAemia at presentation predicted PASC, conditional on patient demographics and initial disease severity (OR 1.31 [95% CI, 1.08 – 1.59], p=0.007 (Supplement)). The association was strongest for patients with moderate disease severity at presentation (Figure), with 78.6% (22/28) of initially RNAemic patients symptomatic in the post-acute phase, compared to 45.5% (35/77) of non-RNAemic patients (difference = 33.1% [95% CI, 11.8% - 54.4%], p=0.005). This difference was due almost entirely to persistent or new respiratory symptoms (difference in proportions = 28.2% [95% CI, 8.4% - 47.9%], p=0.002).

Discussion

To our knowledge, this study describes the first reported association between SARS-CoV-2 RNAemia and PASC. RNAemia at presentation was associated with new or persistent symptoms at least 21 days after symptom onset independent of initial patient severity and the association was strongest among patients with moderately severe clinical presentations requiring hospital admission. This finding adds to the growing literature on SARS-CoV-2 RNAemia's role in disease severity and extrapulmonary complications in the acute phase of illness, as well as the association between hospitalization and PASC (1,2,5,6). The incidence of PASC was lower in this single-center study than in reports from Italy and the UK (3,4), but similar to that reported in a recent study from the US (9). The potential contributions of patient characteristics, study

129 methodologies, and viral variants to these discrepancies merit further study. Though the
130 mechanisms underlying RNAemia's contributions to multi-system pathology in both the acute
131 and post-acute phases, when persistent, remain to be elucidated, mounting evidence for its
132 predictive value suggests that testing for SARS-CoV-2 RNAemia at presentation may help guide
133 the triage, management, and prognosis of COVID-19.

134
135 **Acknowledgements:** The authors would like to thank the additional author members of the
136 Stanford COVID-19 Biobank Study Group include: Elizabeth J Zudock, Marjan M Hashemi,
137 Kristel C Tjandra, Jennifer A Newberry, James V Quinn, Ruth O'Hara, Euan Ashley, Rosen
138 Mann, Anita Visweswaran, Thanmayi Ranganath, Jonasel Roque, Monali Manohar, Hena Naz
139 Din, Komal Kumar, Kathryn Jee, Brigit Noon, Jill Anderson, Bethany Fay, Donald Schreiber,
140 Nancy Zhao, Rosemary Vergara, Julia McKechnie, Aaron Wilk, Lauren de la Parte, Kathleen
141 Whittle Dantzler, Maureen Ty, Nimish Kathale, Arjun Rustagi, Giovanny Martinez-Colon, Geoff
142 Ivison, Ruoxi Pi, Maddie Lee, Rachel Brewer, Taylor Hollis, Andrea Baird, Michele Ugur, Drina
143 Bogusch, Georgie Nahass, Kazim Haider, Kim Quyen Thi Tran, Laura Simpson, Michal Tal, Iris
144 Chang, Evan Do, Andrea Fernandes, Allie Lee, Neera Ahuja, Theo Snow, James Krempski. We
145 would also like to thank Hien Nguyen, Lingxia Jiang, and Paul Hung from COMBiNATi Inc. for
146 all the material and technical support.
147
148 **Disclosures:** Yang is a Scientific Advisory Board member of COMBiNATi Inc.

149
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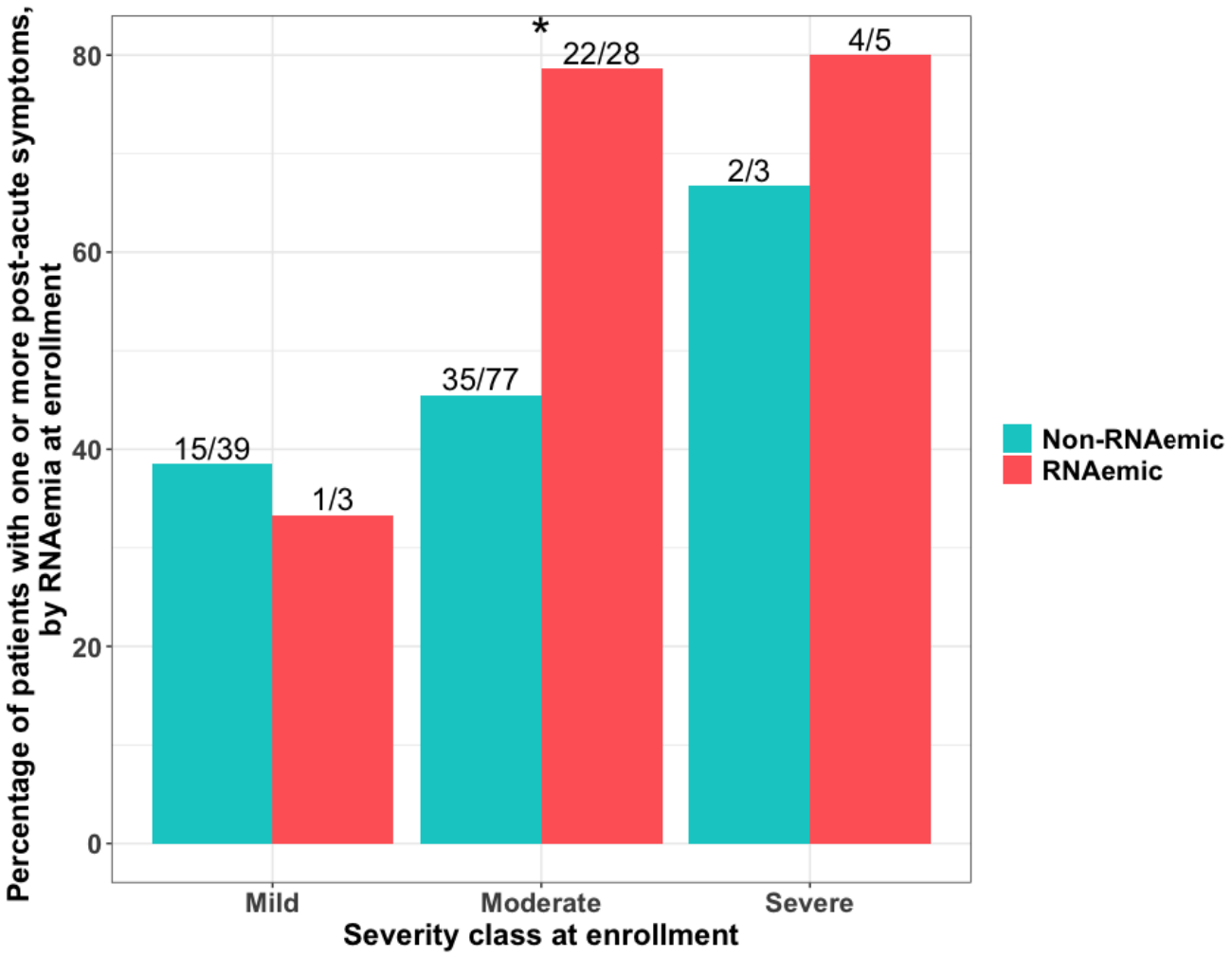
Tables and Figures

Table: Progression of COVID-19 symptoms

Symptom	On enrollment	Persistent at follow-up	New at follow-cup
Cardiovascular			
Chest Pain	34.2% (53/155)	11.3% (6/53)	0.7% (1/149)
Palpitations	0.6% (1/155)	0 (0)	1.3% (2/155)
Dermatologic			
Rash	1.3% (2/155)	0 (0)	0.6% (1/155)
Hair Loss	0 (0)	0 (0)	0.6% (1/155)
Gastrointestinal			
Nausea/vomiting/diarrhea	43.8% (68/155)	7.3% (5/68)	0.7% (1/150)
Constitutional			
Fever	64.5% (100/155)	1.0% (1/100)	0 (0)
Chills	32.9% (51/155)	3.9% (2/51)	0.6% (1/153)
Myalgia	41.2% (64/155)	15.6% (10/64)	4.1% (6/145)
Fatigue	36.7% (57/155)	14.0% (8/57)	8.2% (12/147)
Neuropsychiatric			
Loss of Taste	41.2% (64/155)	14.0% (9/64)	0 (0)
Loss of Smell	29.6% (46/155)	19.5% (9/46)	0 (0)
Confusion	2.5% (4/155)	0 (0)	2.6% (4/155)
Headache	22.5% (35/155)	2.8% (1/35)	5.2% (8/154)
Dizziness	5.8% (9/155)	22.2% (2/9)	2.6% (4/153)
Insomnia	0.6% (1/155)	0 (0)	0.6% (1/155)
Anxiety	0 (0)	0 (0)	1.3% (2/155)
Respiratory			
Cough	72.2% (112/155)	25.8% (29/112)	3.9% (5/126)
Shortness of breath	65.1% (101/155)	18.8% (19/101)	3.7% (5/136)

191 **Figure**



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193 **Figure. Rate of post-acute sequelae of SARS-CoV-2 infection, by RNAemia and clinical**
194 **severity on enrollment.** Overall, 75.0% (27/36) of initially RNAemic patients had one or more
195 post-acute symptoms at follow-up, compared to 43.7% (52/119) of non-RNAemic patients
196 (difference = 31.3% [95% CI: 12.8% - 49.8%], p=0.002). Conditional on severity at enrollment
197 (mild = discharged from ED [n=42], moderate = hospitalized, requiring no more than oxygen by
198 nasal cannula [n=105], severe = hospitalized, requiring high-flow nasal cannula or mechanical
199 ventilation [n=8]), RNAemia on presentation was associated with significantly higher rates of

PASC for presentations of moderate severity (difference = 33.1% [95% CI, 11.8% - 54.4%], p=0.005). * indicates p-value<0.05.