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Case report

Case series: Failure of imaging & biochemical markers to capture disease progression in COVID-19

Zachariah L. Dorey-Stein [a,*], Catherine N. Myers [a], Maruti Kumaran [b], Albert J. Mamary [a], Gerard J. Criner [a]

[a] Department of Thoracic Medicine and Surgery, Lewis Katz School of Medicine at Temple University, Philadelphia, PA, USA
[b] Department of Radiology, Lewis Katz School of Medicine at Temple University, Philadelphia, PA, USA

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ABSTRACT

We report four individuals admitted for acute respiratory failure due to COVID-19 who demonstrated significant clinical improvement prior to discharge and subsequently were readmitted with worsening respiratory failure, elevated inflammatory markers and worsening chest imaging. We propose a multi-disciplinary discharge criterion to establish a safer discharge process including trending inflammatory markers, daily imaging and pursuing follow up CT chest, particularly in individuals with significant morbidities and health disparities.

1. Introduction

COVID-19 related hospitalization affected 50/100,000 of the United States population by early May 2020. A recent report of a large cohort of NYC COVID-19 related hospitalizations described a hospital discharge rate of 78.5% with 2.2% hospital readmission [1].

Presently it is unclear what criteria should be met prior to discharging patients diagnosed with COVID-19 in order to minimize readmission rates. In this case series we report four individuals admitted for acute respiratory failure due to COVID-19 who demonstrated significant clinical improvement prior to discharge and subsequently were readmitted with worsening respiratory failure and significant new findings on admission computed tomography (CT) of the chest. We hypothesize why these patients were readmitted and postulate a multidisciplinary discharge criterion to establish a safer discharge process.

2. Cases description

2.1. Case 1

61-year-old female with a past medical history of schizophrenia was admitted from a residential mental health facility with shortness of breath and subjective fevers. Nasopharyngeal swab for COVID-19 performed at the facility was positive. On admission she was febrile with a new 2-L requirement. Admission labs were notable elevated inflammatory markers (Tables 1 and 2). CT chest showed diffuse peripheral predominant bibasilar and right upper lobe ground glass opacities (Fig. 1). She received ceftriaxone and azithromycin, methylprednisolone 125 mg daily, and was considered an appropriate candidate to enroll in clinical trials however a legal authorized representative could not be identified.

Due to an increasing oxygen requirement, rising inflammatory markers, and a worsening left upper lobe opacity she was treated with methylprednisolone 500 mg daily and hydroxychloroquine for presumed cytokine storm. Inflammatory markers improved, oxygen requirement decreased from 5 to 3 L and chest x-ray on day of discharge to a short-term nursing facility showed mild improvement in aeration of left perihilar infiltrate and an unchanged right infiltrate.

She returned to the hospital within 24 hours obtunded, requiring a non-rebreather and was admitted to the intensive care unit. Admission labs revealed new lymphopenia and escalating inflammatory markers (Tables 1 and 2). CTA of the chest ruled out pulmonary embolism and showed worsening nodular ground glass opacities in the upper lobes (Fig. 1). She was treated with methylprednisone 125 mg daily and sarilumab subcutaneously for cytokine storm. Hydroxychloroquine was discontinued and her mentation returned to baseline. Over the next week she clinically improved, her oxygen was weaned to 2 L and she was discharged back to her residence to complete a 10-day course of prednisone 30 mg daily.

* Corresponding author. Department of Thoracic Medicine and Surgery, Lewis Katz School of Medicine at Temple University, 3401 North Broad Street, Philadelphia, PA, 19140, USA.
E-mail address: zachariah.dorey-stein@tuhs.temple.edu (Z.L. Dorey-Stein).

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Table 1
Demographics.

	Case 1	Case 2	Case 3	Case 4
Age (years)	61	72	78	51
Gender	Female	Male	Male	Female
Race	African-American	Asian	Caucasian Non-Hispanic	Caucasian Hispanic
Supplemental O2 at discharge (liters)	2	3	none	none
Resolution of CXR abnormality at discharge	Partial resolution	Unchanged	Unchanged	Unchanged
Length of stay (days)	6	3	3	1
Days to readmission	1	15	8	5
Length of Readmission (days)	7	6	18	4
Readmission imaging	Worse ground glass opacities	Extensive bilateral ground glass consolidation	Progression of peripheral ground glass and crazy paving	Progression of peripheral upper lobe predominant ground glass
Readmisson SaO 2 (%)	86	95	84	98
Readmission O2 requirement (L)	55 l 100% FiO2	30l 100% FiO2	7	none

Table 2
Admission and readmission laboratory values.

	Case 1		Case 2		Case 3		Case 4	
Laboratory values	Admission	Readmission	Admission	Readmission	Admission	Readmission	Admission	Readmission
WBC (4.0–11.0 K/mm3)	5.1	8.4	5.1	9.8	12.4	8.6	5.5	8.0
Abs. lymphocyte count (1.0–4.8 K/mm3)	1.6	0.9	0.7	1.1	1.3	1.7	1.5	1.9
Serum Na (136–145 mmol/l)	142	142	136	133	134	140	136	136
Creatinine (0.80–1.30 mg/dL)	0.86	0.90	1.38	1.07	1.63	1.59	0.86	0.88
D-dimer (0–500 ng/mL)	1369	1532	886	14,508	1200	54,165	300	362
CRP (0.0–0.4 mg/dL)	7.5	3.5	6.2	7.7	12.3	1.0	0.9	3.64
Ferritin (8–388 ng/mL)	213	233	393	1821	371	455	203	269
Triglycerides (<150 mg/dL)	157	190	75	153	123	338	123	175
Fibrinogen (200–385 mg/dL)	373	380		719	329	231	329	585
LDH (87–247 U/L)	439	366	266	305	181	341	201	218
PT (10.6–13.7 sec)	13.3	13.4		14.2	11.3	14.1	11.3	12.3
aPTT (27.0–37.7 sec)	32.2	23.2		29.3	34.8	28.4	34.8	30.7
INR	1.1	1.1		1.2	0.9	1.2	0.9	1.0
IL-6 (<5.00 pg/mL)			47.75			1764.22		1.69
IL-1 Beta (<3.9 pg/mL)			<3.9			<3.9		<3.9
IL-10 (<2.00 pg/mL)			1.8			4.4		1.6

2.2. Case 2

72-year-old man past medical history of COPD, ischemic stroke, and bipolar disorder was admitted from a nursing home with three days of fever, dyspnea and myalgia. At the time of admission, he had a low-grade fever and a new 4-L oxygen requirement. Admission labs were notable for lymphopenia, mildly elevated inflammatory markers and positive nasal swab (Tables 1 and 2). CT chest was unremarkable (Fig. 2). He was treated for a COPD exacerbation with oral prednisone and azithromycin and discharged on the third day of his admission despite CRP remaining elevated and a new 3 L of oxygen. Other inflammatory laboratory work was not trended nor was imaging performed after the day of admission.

He was readmitted 15 days later with acute on chronic hypoxemic

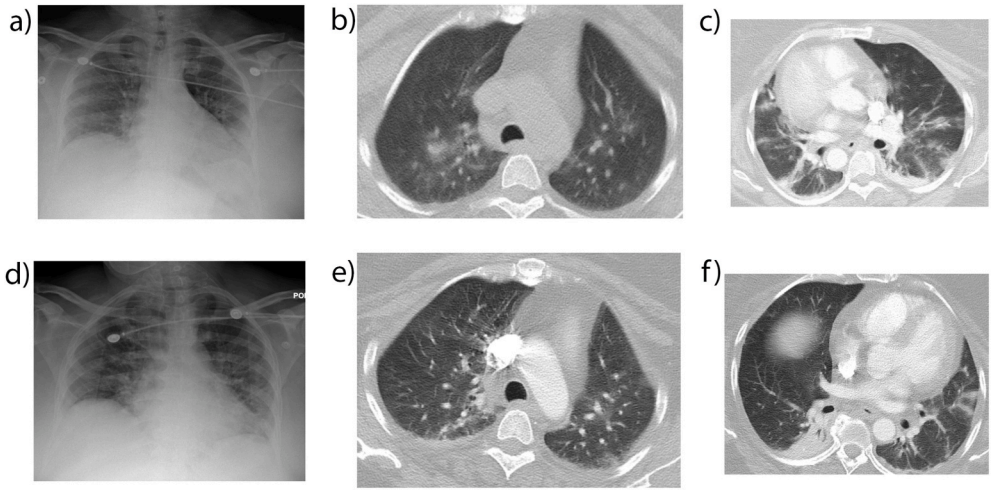

Fig. 1. 1A, 1B and 1C (From left to right clockwise): Admission CXR shows low lung volumes with left lower lobe peripheral parenchymal opacities. CT shows right upper lobe and bilateral lower lobe nodular areas of peribronchovascular and peripheral airspace opacification.
Fig. 1D, E and 1F (From left to right clockwise): Readmission imaging with features of worsening basilar predominant interstitial thickening and right lower lobe atelectasis and central and peripheral areas of ground glass opacities.

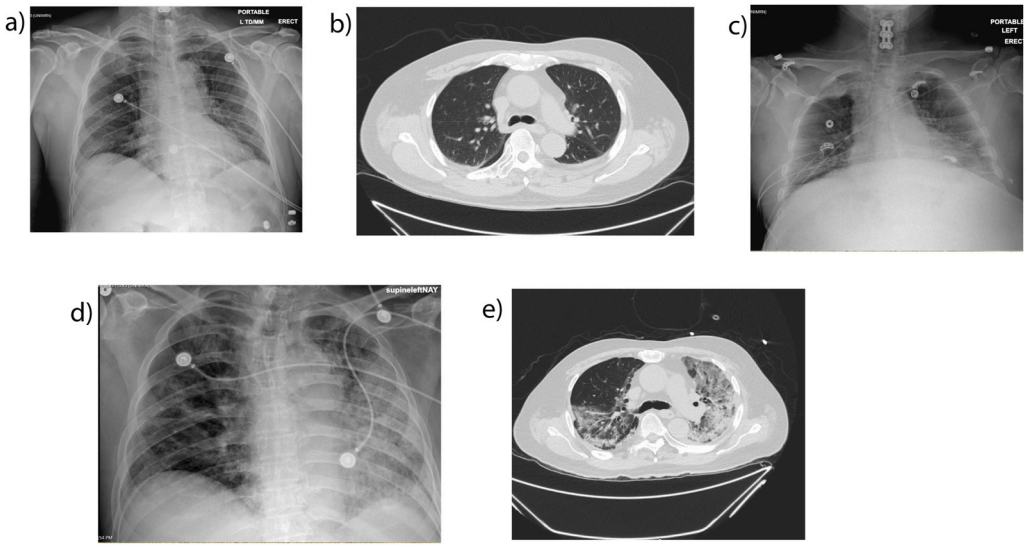

Fig. 2. 2A & 2B (clockwise from left to right): Admission CXR with bilateral atelectasis. Admission CT chest notable for mild airway inflammation and bilateral trace pleural effusions.
Fig. 2C: Discharge CXR is unchanged.
Fig. 2D and E and (From left to right): Readmission CXR with diffuse patchy airspace disease throughout the left lung and moderate patchy airspace disease in the right lung markedly progressed. Readmission CT chest with extensive multifocal GGO.

respiratory failure requiring a non-rebreather. Readmission labs were notable for persistently elevated inflammatory markers (Tables 1 and 2). CT chest showed extensive patchy multifocal consolidations with ground glass bilaterally (Fig. 2). He received empirical broad-spectrum antibiotics, methylprednisolone 500 mg daily and IVIG for three days to treat for cytokine storm. His oxygen requirement was weaned to 3 L and inflammatory markers trended down, and he was discharged on the sixth day of his admission back to a skilled nursing facility to complete a 6-day course of prednisone 40 mg daily.

2.3. Case 3

78-year-old male past medical history notable for diabetes mellitus type II and coronary artery disease presented with one month of dry cough. A chest x-ray performed the day prior to presentation demonstrated bilateral airspace opacities and led to him being referred to the emergency department. At time of admission he was afebrile with an oxygen saturation of 90% on room air. Laboratory work was notable for a leukocytosis without lymphopenia (Tables 1 and 2). CT chest demonstrated multifocal ground glass opacities most pronounced in the right upper lobe (Fig. 3).

During the patient's four-day hospitalization he received ceftriaxone, azithromycin, prednisone 40 mg daily and enrolled in a double-blind clinical trial for sarilumab. He was weaned off supplemental oxygen, inflammatory markers trended down, but chest x-ray on day of discharge demonstrated worsening bilateral interstitial opacities.

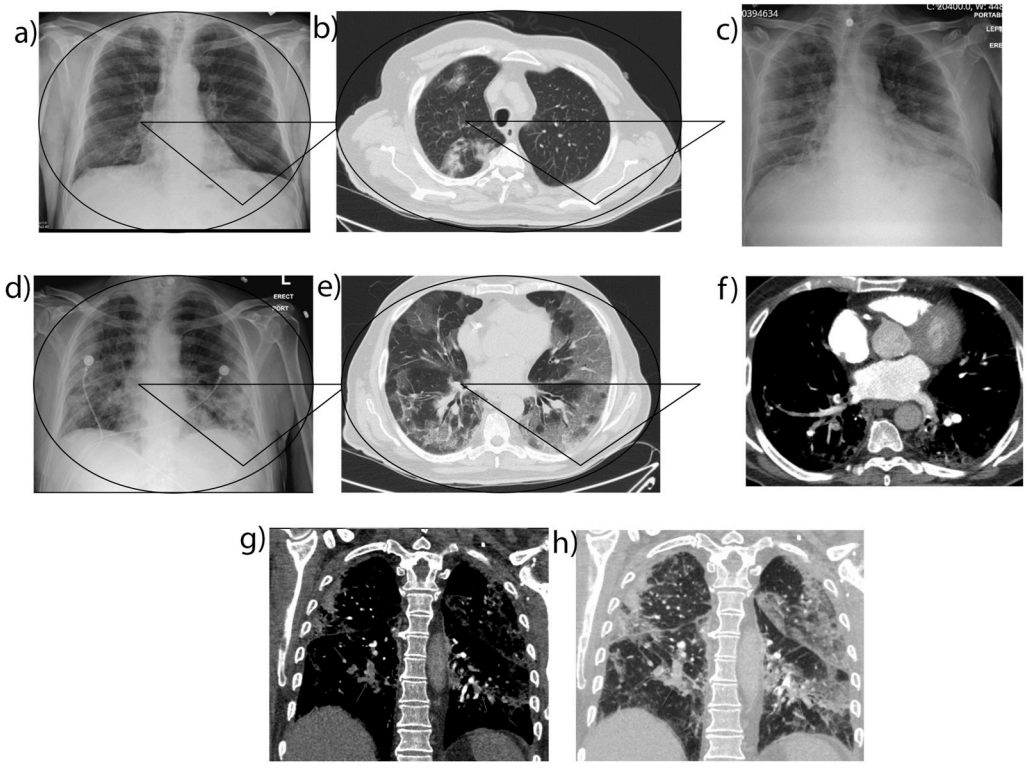

Fig. 3. 3A & 3B (left to right clockwise): Admission CXR with nodular right upper lobe opacity. Admission CT chest showing multifocal peripheral distribution of GGO.
Fig. 3C: Discharge CXR showing improved right upper lobe opacity with linear atelectasis at the bases.
Fig. 3D and E and (left to right): Readmission CXR with patchy bilateral opacities. Readmission CT chest demonstrates diffuse GGO with crazy paving.
Fig. 3F, G & 3H: CT angiogram shows features of bilateral lower lobe thrombi Readmission CT chest demonstrates diffuse GGO with crazy paving.

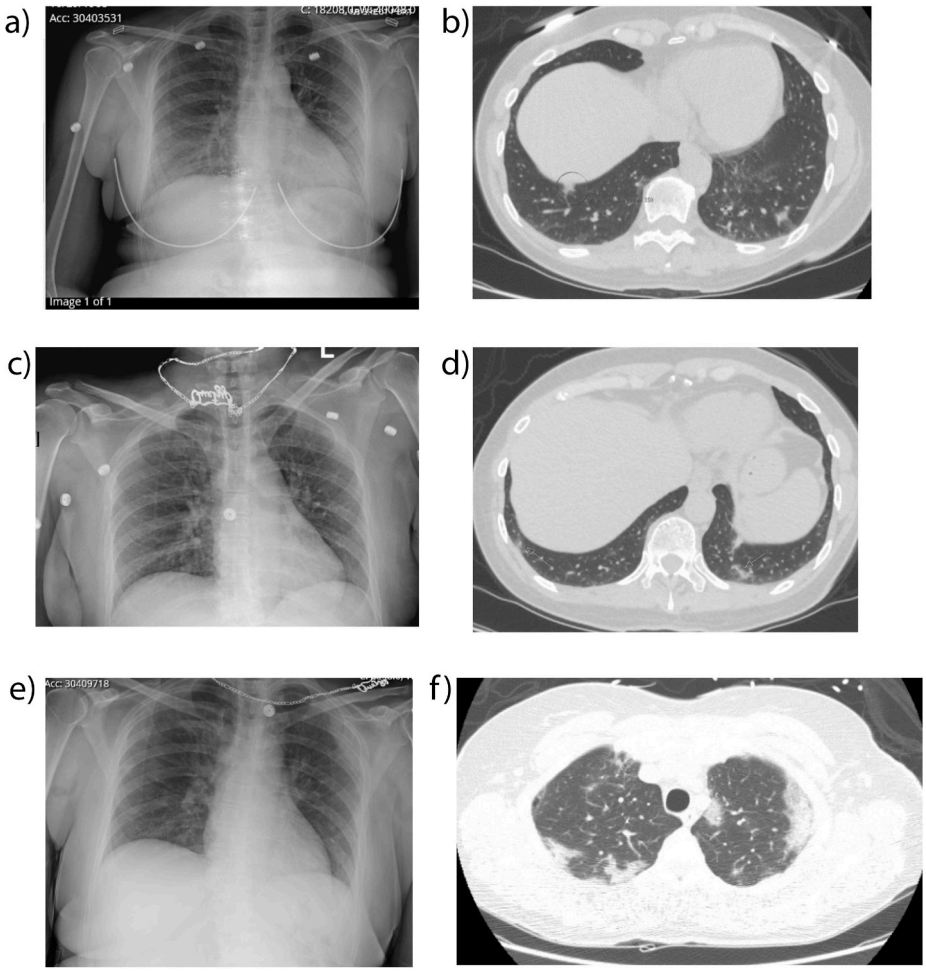

Fig. 4. 4A, 4B, 4C, 4D (From left to right clockwise): Admission CXR with bibasilar opacities. CT Urogram with images of the lung bases demonstrate peripheral subpleural ground glass nodules as highlighted Fig. 4D: CXR from day of discharge unchanged.
Fig. 4D and E: Readmission CXR with mild increase in left upper lobe and bibasilar opacities. CT chest on readmission reflects bilateral GGO.

However, given his overall clinical improvement the patient was discharged home with supportive measures.

The patient was readmitted eight days later with and a new 7-L oxygen requirement. Blood work was significant for an acute kidney injury and elevated d-dimer (Tables 1 and 2). CT chest showed progression of diffuse ground glass opacities with crazy-paving (Fig. 3).

He was treated with broad-spectrum antibiotics, methylprednisolone 500mg daily for three days and reenrolled in the sarilumab trial to treat for cytokine storm. Due to his hypoxia not resolving CTA of the chest was obtained and demonstrated bilateral lobar and subsegmental pulmonary emboli and he was therapeutically anticoagulated. He was discharged home with a new 5-L oxygen requirement. Due to CXR reflecting persistent predominant bibasilar patchy airspace disease a CT chest has been ordered to evaluate resolution of this abnormality.

2.4. Case 4

A 51-year-old female underwent elective CT urography for evaluation of hematuria with incidental finding of peripheral bibasilar ground glass and consolidative opacities and was referred to the hospital for additional evaluation. Vitals were notable for a low-grade fever with no oxygen requirement. CT chest showed diffuse bilateral peripheral ground glass opacities (Fig. 4). Admission labs were unremarkable (Tables 1 and 2). She was started on a five-day course of ceftriaxone, azithromycin and prednisone and discharged the next day.

The patient was readmitted five days later with worsening cough, nausea, vomiting and diarrhea. She was afebrile and had no oxygen requirement. CT chest showed worsening bilateral, subpleural patchy ground glass opacities (Fig. 4). She was enrolled in a clinical trial for remdesivir, the novel anti-viral medication, and restarted on low dose prednisone and azithromycin. She was discharged on the fourth day of her admission to complete one week of prednisone and 5-day course of azithromycin. CXR performed day of discharge showed persistent bilateral opacities that had mildly improved prior to discharge.

3. Discussion

In each case described above an individual was discharged following clinical or radiographical improvement only to be readmitted in a more critical state requiring more hospital resources and medical management. We propose a multi-disciplinary approach to safely discharging individuals in order to reduce readmissions.

First, patients should be afebrile for a minimum of 24 hours and presenting symptoms should have improved prior to considering discharge. Daily inflammatory markers such as d-dimer, fibrinogen, ESR and CRP should have a trend towards resolution. If markers have not resolved or hypoxemia is persistent one should consider other etiologies including pulmonary embolism, bacterial infection, or cytokine storm. CXR should be performed to confirm resolution of opacities prior to considering discharge. Daily chest imaging may have led to the patients in case 2 and 4 not being discharged without further inpatient medical care as their readmission imaging showed significant progression of

ground glass opacities. In contrast, while case 3 clinically improved initially, their imaging worsened suggesting progression of disease that was clinically lagging. Rather than discharging this patient, considering advanced immunomodulatory therapy or alternative diagnoses may have been more prudent in hindsight. Lastly, clinicians should hold a high degree of suspicion and caution for vulnerable populations with known higher mortality including the elderly and individuals with significant comorbidities or health disparities prior to considering discharge.

Collectively, these four cases represent individuals who clinically appeared to be stable or improving but had imaging or biochemical markers on readmission consistent with development of multi-system organ dysfunction or cytokine storm. Each individual would have benefitted from more aggressive treatment with corticosteroids or immunomodulatory therapy prior to considering discharge on their initial admission. In order to limit morbidity, mortality and readmission rates, especially in vulnerable populations with significant health disparities, we recommend assessing for clinical improvement in conjunction with resolving imaging and biochemical markers prior to discharge. Lack of resolution should trigger clinicians to repeat CT Chest in patients diagnosed with COVID-19. If the patient has developed more ground glass opacities consistent with progression of COVID-19 they may benefit from immunomodulatory therapy or imaging findings may represent another process that would explain their hypoxic respiratory failure such as a pulmonary embolism or bacterial pneumonia that warrants treatment.

Author statement

Dr. Dorey-Stein contributed to case series concept and design, data collection, analysis, interpretation of data and drafting and revision of the manuscript. Dr. Criner served as the guarantor of the case series contributing to study concept and design, analysis, interpretation of data, and critical revision and approval of the final manuscript. Dr. Myers contributed to data collection, analysis, interpretation of data and drafting of manuscript. Dr. Kumaran contributed to imaging selection. Dr. Mamary contributed to revision of the paper.

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Declaration of competing interest

This research did not receive grants from any funding agency in the public, commercial or not-for-profit sectors. There were no study sponsors. The content of this publications solely the responsibility of the authors.

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