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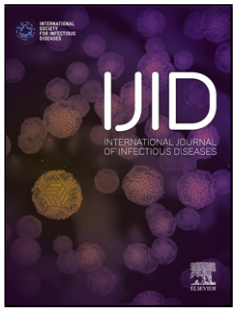

Impact of the coronavirus 2019 (COVID-19) on vasooclusive crisis in patients with sickle cell anaemia

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Impact of the coronavirus 2019 (COVID-19) on vasooclusive crisis in patients with sickle cell anaemia.

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Highlights

- COVID-19 in Sickle cell disease (SCD) patients is thought to be mild to moderate in severity.
- Symptoms like fever, cough, fatigue, abdominal pain and anosmia are common presenting features of COVID-19 in SCD.

- Haemoglobin, lymphocyte subset, platelets, and reticulocytes, were reduced in COVID-19 positive group, whereas, the LDH and ferritin were significantly elevated.
- COVID-19 had no significant impact on mortality or morbidity in patients with SCD.

Abstract:

Objectives: The aim of this study was to assess the impact of COVID-19 on the morbidity and mortality on vasooclusive crisis (VOC) in sickle cell anaemia (SCA) patients.

Methods: One hundred patients with(fifty) or without COVID-19 PCR positivity(fifty), were enrolled in a prospective cohort study after signing a written informed consent.

Results: The COVID-19 positive patients had significantly higher median VOC episodes/year i.e 3 /year (IQR, 1-6 /year) v/s 2 /year (IQR, 2-12 /year) ($p<0.05$) respectively, however the need for hospitalization was similar. There was a higher culture proven infection in COVID-19 negative group (P= 0.05). COVID-19 positive group had more osteonecrosis ($p<0.05$), splenic sequestration, splenomegaly, and hepatic crisis (P values 0.05, 0.006 and 0.02 respectively). Symptoms of fever, cough, fatigue, abdominal pain and anosmia were significantly higher ($p<0.05$) in the COVID-19 positive patients. Both cohorts, showed a fall in the mean haemoglobin, lymphocyte subset, platelets, and reticulocytes, whereas, the LDH and ferritin were significantly elevated. In SCA COVID-19 positive patients the rise in WBC, reticulocyte%, platelets, and ferritin was subdued ($p<0.05$). Two died in COVID-19 positive, whereas three died in the COVID-19 negative, without statistically significant difference in mortality.

Conclusions: Although COVID-19 infection may have triggered the onset of VOC, it did not significantly influence the morbidity or mortality in this SCA cohort.

Keywords: Sickle cell anaemia; SCA; COVID-19; Coronavirus; Vasooclusive crises

Introduction

Coronavirus disease 2019 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Gorbalenya et al,2020). COVID-19 has currently spread to 191 countries and all the continents (https://coronavirus.jhu.edu/map.html) with the pandemic showing no signs of coming under control, in spite of all the efforts by the entire world. This has resulted in an unprecedented number of deaths globally, with widespread lockdowns and disruption of world economies and businesses (Fauci et al,2020). The clinical features of SARS-CoV-2 varies from mild in about 80%, severe in 15%, and critical in 5%, with more severe illness seen predominantly in the adults with advanced age, and those with underlying comorbidities, although it is reported at all ages (Wu Z, and McGoogan JM, 2019). Sickle cell anaemia (SCA) patients are prone to pulmonary complications such as acute chest syndrome (ACS) and thromboembolic complications (Steinberg MH,1999). Owing to the underlying immunocompromised state, SCA patients are also at a higher risk of overwhelming inflammation and cytokine associated lung injury (Hussain et al, 2020). COVID-19 has been reported in persons with SCA, and has a variable outcome on the morbidity and mortality (Beerkens et al, 2020; Chakravorty et al,2020; de Sanctis et al, 2020; Nur et al, 2020; Odièvre et al, 2020). Vaso-occlusive crisis (VOC) is among the commonest manifestations of SCA, that brings patients for medical facilities. Impact of COVID-19 is not clear on morbidity and mortality associated with SCA VOC. We prospectively enrolled SCA patients who presented to the emergency department, with VOC and had signs and symptoms suggestive of COVID-19. All of the patients were tested for the presence of COVID-19 by RT-PCR, during their accident & emergency department (A&E) visits for painful VOC over the study period of 6 months.

Material and methods

Design & setting

In this prospective cohort study, we enrolled consecutive SCA patients presenting with VOC to the A&E, after an informed consent following the approval by our local medical research and ethics committees.

Population

SCA patients presenting with VOC and signs and symptoms suggestive of COVID-19, with a confirmed positive RT-PCR represented the cases, whereas, those who tested negative for COVID-19, formed the control study group. Some of the COVID-19 negative patients presented on multiple occasions with painful sickle crisis during the study period.

Outcomes

Our data collection included demography, previous SCA-related complications, other comorbidities, presenting signs and symptoms, baseline laboratory findings including haematological tests (haemoglobin, WBC, platelets, HbF, HbS and HbA2), biochemical test including renal, hepatic function, serum ferritin (S. Ferritin) and lactate dehydrogenase (LDH). We have also collected their laboratory data at the time of presentation for their current episode, and captured the medical therapy they received and the ensuing outcome. Complete blood counts were obtained using Sysmex XN9100 automated blood cell counter (SYSMEX, Europe GmBH, Hamburg Germany) within 4-12 hours of collection, and high-performance liquid chromatography (HPLC) was done using the Bio-Rad VARIANT II™ instrument (Bio-Rad Laboratories, Hercules, CA, USA) applying the "β-thalassemia short program". RT-PCR for COVID 19 was performed using the QuantStudio 5 Real-Time PCR System (Applied Biosystems, Life Technologies, and Foster City, CA, USA). Additionally, emergency cases were done using the GeneXpert machine (Cepheid, Sunnyvale, CA USA)

according to the manufacturer's instructions and in accordance with the national case definition and clinical guidelines in the Sultanate of Oman.

Statistics

We used descriptive statistics and univariate comparisons with the $\chi 2$ test to determine differences between SCA patients with and without COVID-19. Paired and unpaired Students t test were used to compare continuous variables. The primary outcome was to see the impact of COVID-19 on VOC in SCA with a p-value of <0.05 was considered statistically significant.

Results

Table 1a shows the demographical data, medical history, clinical presentation, treatment and outcome in this study cohort. Fifty patients were confirmed COVID-19 RT-PCR positive (n=50 episodes), whereas the remaining 50 patients were COVID-19 RT-PCR negative, with some of these patients presenting on multiple occasions with painful sickle crisis during the study period (n=67 episodes).

The severity of SCD patients were classified as mild, moderate, and severe based on the number of VOC/year as 0-3, >3 up to 6 and more than 6 VOC episodes per year. The COVID-19 positive patients in this study cohort had a significantly higher median VOC episodes/year i.e 3/ year (IQR, 1-6 /year) v/s 2 /year (IQR, 2-12 /year) ($p<0.05$; Mann-Whitney test) respectively. However, there were no significant differences in the age, or gender between the two. The median length of hospital stay was relatively longer in the COVID-19 negative group, although the percentage of admissions was similar in both groups. Sickle β^0 were found to be more likely to get COVID-19 infection than HbSS patients ($p<0.009$, Chi square test). Considering previous comorbidities, COVID-19 negative group showed a higher culture proven infection ($p= 0.05$, Chi square test), with significantly higher history of bacterial and viral infections (p

= 0.04 for both). COVID-19 positive group were more likely to have more osteonecrosis of joints ($p<0.05$, Chi Square test), splenic sequestration, splenomegaly, and hepatic crisis (P values 0.05, 0.006 and 0.02, Chi Square test respectively). Intermittent simple blood transfusions were relatively higher in the COVID-19 positive group, but 6% of the COVID-19 negative group were on regular transfusions.

Amongst the presenting symptoms, fever, cough, fatigue, abdominal pain and anosmia were significantly higher ($p<0.5$, Chi-Square test) in the COVID-19 positive patients. The clinical course in the two groups indicated that COVID-19 positive group had a relatively milder severity with pain less frequently seen in this group. Although the admission rates were similar in both groups, a relatively higher number of ICU admissions and requirement for ventilator support was observed in the COVID-19 negative group.

In both the SCA cohorts, there was a fall in the mean haemoglobin, lymphocyte subset, and platelets, whereas, the mean S.LDH and S ferritin were significantly elevated ($p<0.5$, paired students' test) (Table 1B). The mean white cell count and reticulocytes rose significantly in the SCA COVID-19 negative patients during their VOC episodes leading to the A&E visit, but this was not seen in the SCA COVID-19 positive patient cohort. The other significant differences during the presenting episode were lower mean total white cells, lymphocytes, reticulocyte percentage, platelet count, and S ferritin in the COVID-19 positive group (Table 1C). C-reactive protein, fibrinogen and D dimers were elevated, with one confirmed pulmonary embolism in COVID-19 positive, two thrombosis episodes in COVID-19 negative group, but it was not statistically significant.

Therapeutic interventions between the two groups, showed significant differences in the use of azithromycin, and convalescent plasma, otherwise no significant difference noted. Two patients died in COVID-19 positive group, whereas three died in the COVID-19 negative, but the difference in mortality was not statistically significant (Table 1D).

Discussion

Due to the immune compromised status, and the known chest complications of SCA, it was feared that patients with SCA, would be adversely affected by COVID-19, setting the rational for our study. To our best knowledge, this is the first study to evaluate the impact of COVID-19 on the morbidity and mortality in SCA patients presenting with VOCs, where two groups of SCA patients, compared head-to-head.

Our two cohort were comparable in terms of age, gender and the need for hospital admission; however, COVID-19 positive subjects were of the more severe SCA phenotype, as judged by the significantly higher level of VOC frequency per year. Conversely, when comparing previous morbidities between the two groups, we observed a statistically significant higher history of culture proven infections including bacterial and viral in the COVID-19 negative group, which may explain the longer duration of hospital stay.

Interestingly, it was observed that Sickleβ^0 genotype was more represented in the COVID-19 positive patients, with significantly higher HbA2- as expected, but the reason for this is not clear, and mandates a larger study sample to infer on the relevance of this observation. Furthermore, there was a higher prevalence of osteonecrosis, splenic and hepatic complications, among COVID-19 positive group. Although the significance of these findings is not clear and it may relate to higher prevalence of Sickleβ^0 genotype in the COVID-19

positive patients, analogous to the observation reported by Adesina et al (2017) where they showed a higher incidence of osteonecrosis in SCA patients co-inheriting α-thalassemia with SCA. Splenomegaly is generally not seen in adults SCD patients, as spleen is progressively lost in older patients owing to the periodic splenic infarction with splenic atrophy. However, spleens are seen to persist in SCD patients to adult life in patients who also carry the thalassaemia gene in association with the sickle gene mutation, and our population is known to have high prevalence of both alpha and beta thalassemia genes.(Alkindi S, et al 2010).

Among the presenting symptoms, our data showed that fever, cough, fatigue, abdominal pain and anosmia were the leading symptoms ($p<0.5$, Chi-Square test) in the COVID-19 positive patients. This is similar to those seen in the general population and reported amongst sickle cell disease cohorts (Al Wahaibi et al, 2020; Balanchivadze et al, 2020; Khamis et al, 2020). Khamis et al (2020), in their report from the same population, showed that 95.9% cases were mild, 3.6% moderate, and 0.5% severe with the case fatality rate of 0.5% in non SCA population. Furthermore, it is interesting to note that pain was less frequent in COVID-19 positive group, whereas abdominal pain and anosmia were seen only in the COVID-19 positive group, which are also COVID-19 disease defining symptoms in the general population (Aziz et al, 2020). Aziz et al (2020), in their meta-analysis, showed that anosmia is a highly prevalent symptom with an odds ratio of 14.7 in COVID-19 positive patients.

Looking at the laboratory parameters, and comparing the baseline v/s parameters at time of admission, a fall in the mean haemoglobin, lymphocyte subset, and platelets, with elevation in the mean S.LDH and S ferritin were seen ($p<0.5$, paired students' t test) (Table 1B). This indicates bone marrow suppression driven by the inflammatory process, that is classically seen during the SCA VOC episodes, and is also seen in COVID-19 reported cases (Balanchivadze

et al, 2020). The mean white cell count and reticulocytes rose significantly in the SCA COVID-19 negative patients during their VOC episodes leading to the A&E visit, but, surprisingly, this was subdued in the SCA COVID-19 positive patient cohort. Furthermore, there were other significant differences namely, the lower mean total white cells, reticulocyte percentage, platelet count, and S ferritin in the COVID-19 positive group (Table 1C), as compared to COVID-19 negative group. This is a significant observation that can help understand the factors in play during the COVID-19 infection, but needs a detailed analysis of the underlying cytokine interplay to explain the observed differences and should be evaluated with a larger study sample. It is known that numerical and morphological changes within WBC, is associated with severity of COVID-19 infection (Pozdnyakova et al, 2021).

About one third in both groups, were managed at home after A&E visit, and admission rates were similar in both groups with only 2% of COVID-19 positive patients being classified as severe and only 2 patients (4%) needing ICU admission with one patient (2%) requiring ventilatory support. This is in stark contrast with the US study, where Panepinto et al (2020), showed that 69% of people with sickle cell disease who were infected with coronavirus were hospitalized, with 11% being admitted to the intensive care unit, and 7% died.

ACS is a leading cause of death in SCA, and COVID-pneumonia complicate 15-20% of patients with COVID-19(Gladwin MT and Vichinsky E, 2008; Jain et al, 2017; Zhou et al, 2020). The aetiology of ACS is variable and includes infections and thrombosis, the two elements that are prominent in COVID-19 disease. Further, it is important to note that the COVID-19 symptoms, such as fever, desaturation and dyspnea, are often similar to the symptoms of ACS and may affect clinical decisions. However, ACS incidence in this study cohort was not different between the two groups, i.e., 28% v/s 30.8% in the COVID-19

negative group, and similar to what is seen in other respiratory viral infections (AlKindi et al 2020). Similarly, red blood transfusions or exchange were not significantly different and were used in 40.2% and 52% in COVID-19 negative and positive groups respectively. Red cell transfusions remain the mainstay of therapy for patients with SCA, but pose significant clinical challenges. Although SCD alloimmunization remains a serious consequence of blood transfusions that can lead to life-threatening acute and delayed transfusion reactions, however shortage of blood during the pandemic was also another challenge. (Yazdanbakhsh, 2016; Zimring and Hudson, 2016). However, judicious use of red cell exchange may help in ameliorating COVID-19 related pulmonary complications in SCA patients with pulmonary infiltrates (Okar et al, 2020).

Several studies have reported pulmonary embolism and coagulopathy in patients with COVID-19(Balanchivadze et al, 2020; Edler et al, 2020; Lodigiani et al, 2020). Although both SCA and COVID-19 are strongly associated with thromboembolic disease, and we have seen raised CRP, and fibrinogen in both groups, yet only one patient in COVID-19 positive group was confirmed to have pulmonary embolism (PE), and treated with anticoagulation as per the standard protocol (Balanchivadze et al, 2020; Okar et al, 2020). There were two patients with thrombosis in COVID-19 negative group, one PE and second with cerebral sinus thrombosis. The difference between the two groups was not statistically significant. These findings are similar to those reported by other investigators from Detroit (Balanchivadze et al, 2020). Forty-two % of our cohort received LMWH in COVID-19 positive group, as compared to 31.3% in COVID-19 negative group.

Two deaths were reported in the COVID-19 positive group (4%). A 19-year-old presented with headache and had cerebral haemorrhage, but died in the operating room 12 hr after admission

to hospital. The other patient died with COVID related pneumonia, renal failure and occipital infarction. It's interesting to note that both patients had history of asthma previous history of acute chest syndrome (two factors seen even in normal population) and also splenectomy (Al Wahaibi et al, 2020). These results are in keeping with results from France, where mortality was not severe (Arlet et al, 2020). This is thought to be partly due to these patients being young, self-isolate, and there may be a protective effect against COVID-19 driven by cytokine profile (Arlet et al, 2020). Comparatively, with 1499 deaths in the current Oman population of 5,153,946, there are 128,867 PCR-confirmed cases of COVID-19 subjects, indicating 1.16% mortality rate (https://coronavirus.jhu.edu/map.html). The deaths in the COVID-19 negative patients clearly indicate an exaggerated inflammatory response consistent with expectations based on SCA VOC pathophysiology with ensuing multiorgan failure.

In conclusion, although the mortality in this study is higher than the COVID-19 infection rate in the general population, it did not significantly impact the morbidity or mortality of SCA patients with VOC. COVID-19 positive SCA patients did not have a higher risk for a severe disease course, and neither had a high case-fatality rate, as reported elsewhere in the literature (Arlet et al, 2020).

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Disclosure of Conflict of Interests:

The authors report no conflicts of interest relating to the contents of this article. The authors alone are responsible for the content and writing of this article and received no financial support.

Author contributions

All authors have made substantial contributions, have seen, and approved the final version of manuscript. SAK, RAE, AAM, MAM, SYA, GAK, BAR, SAR, JAY, YAW, SAS and MAR, were fully involved in the conception and design of the study, recruitment & care of patients, acquisition of data, or analysis and interpretation of data. SAK, and AVP were instrumental in the drafting the article and critical appraisal before submission.

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Table 1A - Demographic, medical history, clinical presentations, treatment & outcome

Parameter		COVID positive (N=50)	COVID negative (N=67)	P value
Median Age, yr (IQR)		31	31	P=0.85##
Gender		M:F,27:23	M:F;29:21	
Genotype	SS, n (%)	10(20)	28(56)	P=0.07#
	S/β^0, n (%)	29(58)	16(32)	P=0.01#
Treated at	Home, n (%)	16(32)	20(29.8)	P=0.85#
	Admitted, n (%)	34(68)	47(70.2)	P=0.99#
Length of stay	Median, days (IQR)	5(3.5-7.5)	8(5-12)	P=0.18##
Comorbidities	Previous infections, n (%)	23(46)	56(86.5)	P=0.05#
	Bacterial, n (%)	18(36)	47(70.1)	P=0.04#
	Viral, n (%)	13(26)	37(55.2)	p=0.04#
	Fungal, n (%)	9(18)	17(25.4)	P=0.44#
	Median VOC /year,	3	2	P=0.02##
	IQR	1-6	2-12	
	H/o Acute chest syndrome, n (%)	37(74)	39(58.2)	P=0.41#
	Splenectomy, n (%)	21(42)	28(41.8)	P=0.99#
	Cholecystectomy, n (%)	16(32)	15(22.4)	P=0.37#
	Joint Necrosis, n (%)	17(34)	9(13.4)	P=0.03#
	Sequestration, n (%)	2(4)	0(0)	P=0.05#
	Splenomegaly, n (%)	12(24)	3(4.5)	P=0.006#
	Hepatomegaly/Crisis, n (%)	8(16)	2(2.9)	P=0.02#
	Transfusions-Intermittent, n (%)	43(86)	35(52.2)	p=0.08#
	Transfusions-Regular, n (%)	0(0)	4(5.9)	p=0.03#
Presenting Features	Pain, n (%)	32 (64)	55(84)	P=0.023#
	Fever, n (%)	40(80)	26(38.8)	P=0.02#
	Cough n (%)	23(46)	13(19.4)	P=0.02#
	Reduced saturation, n (%)	8(16)	15(22.4)	P=0.47#
	Fatigue, n (%)	14(28)	3(4.5)	P=0.002#
	Tachypnea, n (%)	7(14)	13(19.4)	P=0.51#
	Pharyngitis, n (%)	10(20)	6(8.9)	P=0.13#
	Headache, n (%)	9(18)	4(5.9)	P=0.07#
	Abdominal pain, n (%)	6(12)	0(0)	P=0.001#
	Anosmia, n (%)	6(12)	0(0)	P=0.001#
Clinical Course	Mild, n (%)	24(48)	12(17.9)	P=0.01#
	Moderate, n (%)	18(36)	20(29.8)	P=0.61#
	Severe, n (%)	1(2)	5(7.4)	P=0.20#
Treatment	Transfusions, - Simple n (%)	20(40)	18(26.8)	P=0.28#
	- Red cell Exchange	6(12)	9(13.4)	P=0.84#
	Medication, - HCQ therapy, n (%)	6(12)	4(5.9)	P=0.29#
	- Azithromycin, n (%)	24(48)	16(23.8)	P=0.05#
	- Dexamethasone,	1(2)	0()	P=0.16#
	n(%)	7(14)	8(11.9)	P=0.77#
		2(4)	0()	P=0.05#

	- Antiviral therapy, n (%) - Convalescent Plasma, n (%) - Antibiotics, n (%)	34(68)	30(44.7)	P=0.18[#]
	LMWH, n (%)	21(42)	21(31.3)	P=0.41[#]
Outcome	ICU admission, n (%) Ventilated, n (%)	2(4) 1(2)	4(5.9) 4(5.9)	P=0.64[#] P=0.31[#]
	Acute chest syndrome, n (%)	20(40)	20(29.8)	P=0.42[#]
	Mortality, n (%)	2(4)	3(6)	P=0.98[#]

Key: IQR – Interquartile range, [#] Chi Square test (Covid19 positive SCA patients' v/s Covid19 negative SCA patients); HCQ – Hydroxychloroquine; LMWH-low molecular weight heparin

Table 1B - Laboratory features – Baseline and at AE presentation

Parameters at Baseline	**COVID positive (N=50 episodes) (50 patients)**			**COVID negative (N=67 episodes) (50 patients)**		
	Basal	AE visit	[$$] P value	Basal	AE visit	[$$] P value
Hemoglobin, g/dl, **Mean±SD**	9.2±1.05	7.4+1.8	P<0.001[$$]	9.8±1.2	7.9+1.5	P<0.001[$$]
White Cells, $X10^9$/L**, Mean±SD**	9.8±3.8	9.8+1.4	P=0.67[$$]	11.3±2.3	12.8+1.6	P=0.01[$$]
Lymphocytes, $X10^9$/L**, Mean±SD**	3.1±1.4	2.4+1.2	P=0.03[$$]	3.6±1.7	3.13+1.9	P=0.05[$$]
Platelets, $X10^9$/L, **Mean±SD**	350±34	212+23	P<0.001[$$]	333±89	278+56	P=0.009[$$]
Reticulocytes,%, **Mean±SD**	7.5±1.2	5.0+1.3	P=0.004[$$]	6.3±1.3	8.76+1.2	P=0.006[$$]
Lactate Dehydrogenase, u/L **Mean±SD**	420±32	1030±42	P=0.01[$$]	415±57	1009+332	P=0.01[$$]
Ferritin, ng/ml, **Mean±SD**	747±189	1829+78	P=0.006[$$]	2659±215	16191+157	P=0.16[$$]

Key: [##] - Unpaired Students "t" test (Covid19 positive SCA patients' v/s Covid19 negative SCA patients); [$$] - paired Students "t" test (in Covid19 positive & Covid19 negative SCA patients)

Table 1C - Laboratory data at the time of presentation

Parameters during AE contact	**COVID positive (N=50 episodes)**	**COVID negative (N=67 episodes)**	**P value Covid19 Pos v/s Neg**
Hemoglobin g/dl**, Mean±SD**	7.4±1.8	7.9±1.5	P=0.14##
White Cells $X10^9$/L**, Mean±SD**	9.8±1.4	12.8±1.6	P=0.01##
Lymphocytes $X10^9$/L**, Mean±SD**	2.4±1.2	3.13±1.9	P=0.08##
Platelets $X10^9$/L**, Mean±SD**	212±23	278±56	P=0.03##
Reticulocytes %, Mean±SD	5±1.3	8.76±1.2	P=0.008##
Lactate Dehydrogenase, u/L **Mean±SD**	1030±42	1009±332	P=0.93##
Ferritin,ng/ml, **Mean±SD**	1829±78	16191±157	P=0.04##

Basal Hb S (%), Mean+SD	82±8.7	81±7.2	P=0.7##
Baal Hb F (%), Mean+SD	8.5±6.2	10.1±2.3	P=0.24##
Basal Hb A2(%), Mean+SD	5.1±1.2	4.45±1.3	P=0.008##
CRP	80.6±98.3	107.9±125.5	P=0.32
Fibrinogen	4.0±1.9	4.2±1.6	P=0.66
D dimers	13.±17		

Key: ## - Unpaired Students "t" test (Covid19 positive SCA patients' v/s Covid19 negative SCA patients)

Table 1D-Clinical & Laboratory features of patients who died(n=5)

Parameters	**COVID-19 positive(n=2)**		**COVID-19 negative(n=3)**		
Cases	Case 1	Case 2	Case 1	Case 2	Case3
Age, yrs	19	31	24	47	24
Sex	M	M	F	M	F
Clinical features	ACS, splenectomy, asthma	ACS, previous DVT, splenectomy, asthma	Mild VOC	ACS, AVN hips, cholecystectomy, splenectomy	ACS, cholecystectomy,
Presenting feature	Headache, back pain	Back and chest pain	Fever, pain, vomiting, tachypnea, reduced saturation	Back pain, fever, cough reduced saturation	Fever, tachycardia, tachypnea,

Terminal event	Cerebral hemorrhage	COVID pneumonia, left occipital lobe infarction, ACS, renal failure	Overwhelming sepsis	Fat embolism syndrome, septicemia	Gram-negative septicemia with multi-organ failure
Hb baseline, g/dl,	8.5	10.3	7.8	9.8	9.6
Hb at presentation, g/dl,	9.9	8.2	4.4	6.9	7.2
WBC baseline, $X10^9$/L**,**	12.6	12.3		10.6	11.6
WBC at presentation, $X10^9$/L,	14.2	54.2	42.9	6.7	34.5
Platelets baseline, $X10^9$/L,	461	331		268	132
Platelets at presentation, $X10^9$/L,	92	108	137	15	15
Lymphocytes, $X10^9$/L,	5.9	2.8	3.1	1.8	4.4
LDH at presentation, u/L	737	10024		1987	6762
S. Ferritin, ng/ml**,**	1180	392300		61781	76808
CRP, mg/L	41	449	442	405	449
Hb F, %	7.4	2.6	36.3	10.1	12.3
Hb A2, %	5.1	4.4	3.9	6.6	5.3

Key: ACS- Acute Chest Syndrome; AVN- Avascular Necrosis; DVT- Deep vein Thrombosis; LDH – Lactic Dehydrogenase; CRP-C-Reactive Protein;