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TRANSFUSION MEDICINE WILEY

LETTER TO THE EDITOR

Blood transfusion needs in COVID-19 patients: An observational prospective unicentric study

Dear Editor,

In 2019 a severe acute respiratory syndrome (SARS-CoV-2), caused by a novel coronavirus (2019-nCoV), was described in Wuhan City, Hubei Province, China, which then rapidly spread and evolved into a pandemic. As of 5 July 2021, 183,298,109 confirmed cases of coronavirus disease (COVID-19) and 3,971,687 deaths all over the world have been reported.[1] Italy is one of the most involved countries, reaching 4,259,909 confirmed cases (as of 2 July 2021) and 127,566 deaths.[1]

Clinical presentations of SARS-CoV-2 are various. Most infected patients are asymptomatic, others develop mild symptoms like dry cough, sore throat, and fever, with a spontaneous resolution. Some cases evolve into pulmonary oedema, severe pneumonia, acute respiratory distress syndrome (ARDS), and septic shock resulting in organ failure. Most-used treatments are chloroquine and hydroxychloroquine, claimed to block viral entry into cells and have immunomodulatory effects, lopinavir/ritonavir and other antivirals, corticosteroids, anti-cytokines or immunomodulatory agents (tocilizumab, a monoclonal antibody IL-6 receptor antagonist),[2] low-molecular-weight heparin (LMWH) to limit the risk of an associated coagulopathy and disseminated intravascular coagulation (DIC).

The WHO has published guidelines to manage the blood supply in response to the COVID-19 pandemic. The guidance underlines the role of blood services in assessing, planning, and responding to the outbreak. In fact, lockdown and social distancing may lead to limited blood resources. Moreover, while blood transfusion requirement may decrease as the health care system is focused on treating COVID-19 patients, thus deferring other clinical interventions, transfusions will still be necessary for emergency situations and to support COVID-19 patients with severe sepsis.[3]

Critical patients may develop anaemia as a consequence of multifactorial and complex pathogenesis. Phlebotomies and other surgical procedures, coagulopathies, pathogen-associated haemolysis, hypoadrenalism, and nutritional deficiencies, as well as the concomitant administration of different drugs, may cause Haemoglobin (Hb) to drop. Decreased erythropoietin production and/or activity could be the consequence of inflammatory cytokines such as IL-1 and TNF-α.[4] The risk in COVID-19 patients is even higher due to the well-known pro-haemolytic effect of hydroxychloroquine, especially in G6PDH-deficient individuals, even if there are few findings supporting the necessity for G6PDH deficiency screening before starting this drug.

Here we report the results of a retrospective evaluation of blood transfusion supply in patients (pts) affected by COVID-19, admitted to Policlinico Umberto I, Sapienza University of Rome, during the epidemic outbreak, taking into account treatments, comorbidities, clinical and laboratory parameters, especially those related to RBC transfusion.

From the 1 March 2020 to 27 April 2020, 71 patients with COVID-19 infection were admitted to Policlinico Umberto I, in the departments of Infectious Disease or in the intensive care unit (ICU).

Forty-seven of them, required transfusion support; 30 patients were males, 17 were females; median age was 72 (38–95). Sixteen out of 47 (34%) had blood group type A. Forty-five patients required RBC, with a median of 3 transfusions each (1–20); nine patients received plasma support, with a median of 4 transfusions (3–24). Five out of the 45 patients who required RBC, required plasma supply as well; two patients received only plasma. Two patients received platelets, RBC and plasma (see Figure 1D). Thirty-two patients out of 47 (68%) showed comorbidities such as hypertension and cardiovascular diseases (18 patients), diabetes mellitus (nine patients), oncological/haematological diseases (six patients), autoimmune diseases (three patients).

Twenty-two out of the 47 patients who required transfusion, were admitted to ICU due to severe clinical disease. All of them were treated with the same therapy, consisting of anti-viral drugs, LMWH, and hydroxychloroquine (400 mg/day); one patient did not receive hydroxychloroquine due to G6PDH deficiency.

Considering the pro-haemolytic effect of hydroxychloroquine, we monitored haemolytic markers in patients treated with RBC transfusions, observing the following median values: Hb 12.3 g/dl (7.4–16.6) at admission; Hb 7.5 g/dl (6.7–11) and lactate dehydrogenase (LDH) 383 UI/L (271–781, n.v. 125–225) at the time of first transfusion. Both direct and indirect antiglobulin tests were negative in all patients, thus excluding immune-mediated haemolytic anaemia. The median time between COVID-19 diagnosis and transfusion requirement was 13 days (0–33); all patients showed increasing LDH values starting at a median time of 5 days (1–11) after COVID-19 diagnosis and first hydroxychloroquine administration, with a median peak value of 706 IU/L (301–2805).

In more detail, in Figure 1 we report the trend of values of Hb and LDH of the 22 patients (Figure 1A), and day-by-day LDH and Hb profiles and transfusion requirements of two representative patients.

The first patient (Figure 1B) was a 42-year-old female affected by hypertension and autoimmune hepatitis treated with steroids. In 6 days, Hb and LDH values reached 9.8 g/dl and 1000 IU/L, respectively (at admission, Hb 13 g/dl, and LDH 282 UI/L). Fourteen days after, LDH reached 2285 UI/L value. In the same time frame, with the increasing levels

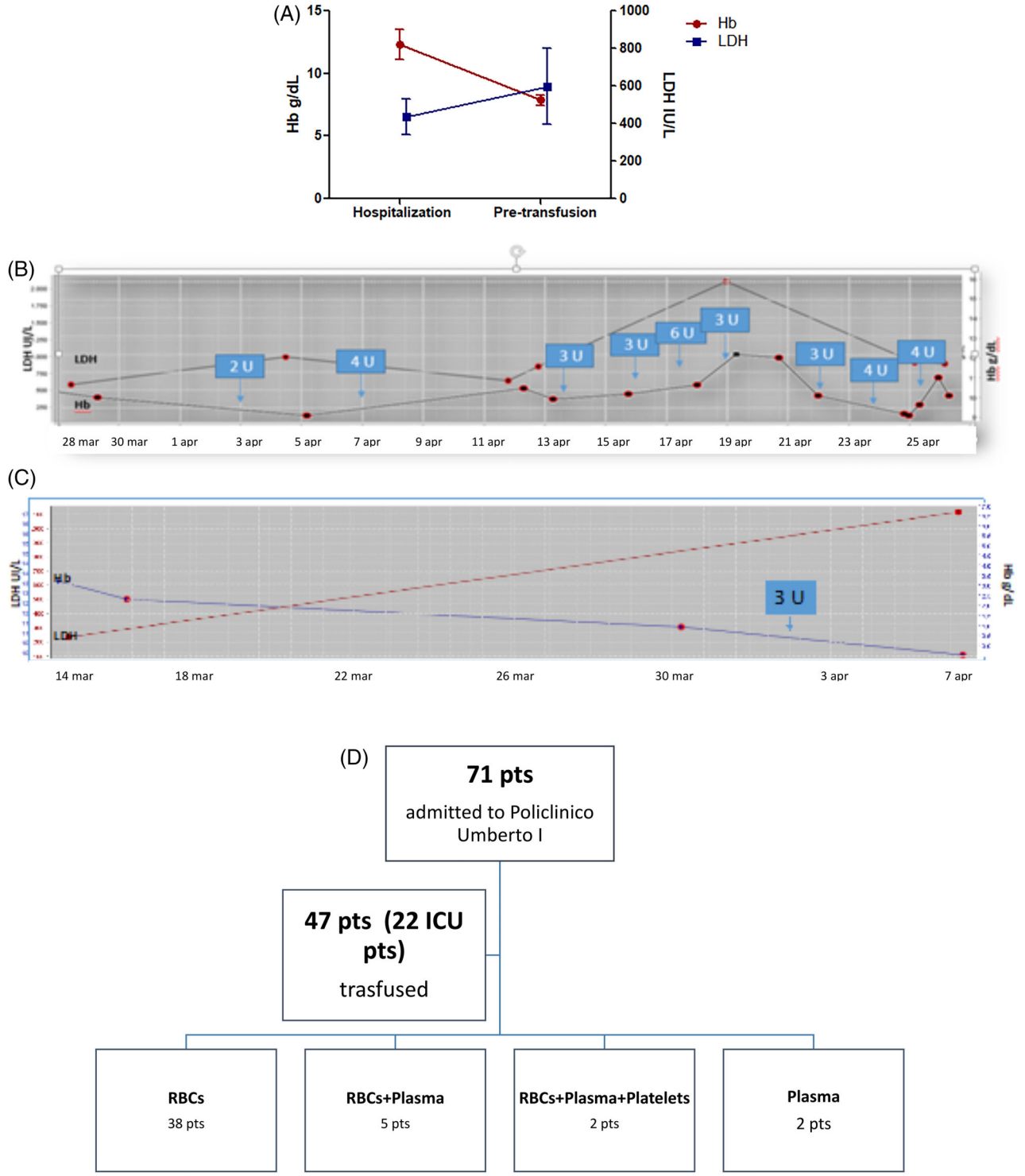

FIGURE 1 The trend of values of haemoglobin (Hb) and LDH of 22 patients (A); LDH, Hb profiles and transfusion requirements of two patients (B,C). Flow-chart of patients enrolled in the study and blood transfusion needs (D)

of LDH, she received 20 RBC units. The second patient (Figure 1C), a 74-year-old male, with ulcerative colitis, hypertension, benign prostatic hyperplasia, and endovascular prosthesis for aortic abdominal aneurysm showed Hb 13.6 g/dl and LDH 255 UI/L at admission. In 18 days, he showed a progressive increase of LDH with a peak of 1100 UI/L.

Overall, at our Institution, in the period analysed, 33.8% of patients admitted to ICU required transfusion support; this data is comparable with other published experiences.[5] We observed a lower request for platelets and plasma with respect to others' reported experiences, maybe reflecting different therapeutic and transfusion

management among patients at different institutions as well as various clinical manifestations and comorbidities.

We compared this 2020 data with those observed in the corresponding period of 2019, noting a lower number of blood products transfused in ICU setting at our Institution. In 2019, there were a total number of transfusion requests for 17 patients, in 16 cases for RBCs, in five cases for plasma and 11 for platelets.

We could suppose that our observations, performed on a larger number of patients with respect to published data, may reflect the role of hydroxychloroquine in the onset of an acute drop in Hb levels, caused by haemolysis.

This effect could be induced by a G6PDH deficiency not yet diagnosed, worsening the critically ill patients' anaemia condition determined by the above-mentioned factors, including the concomitant administration of drugs as well. Notably, the estimated number of G6PDH-deficient individuals is close to 400 million people worldwide, with a global prevalence of 4.9%,[6] highest prevalence in Africa, Asia, Middle East and Mediterranean countries.[6,7] Italian prevalence of G6PDH-deficiency is reported to be 0%–3%, with a higher prevalence among some regions (e.g. Sardinia). A recent Italian prospective study conducted on more than 3000 healthy blood donors identified 1.1% of G6PDH-deficient individuals, characterised by haematological parameters of G6PDH within the normal range.[7]

In other kinds of interstitial pneumonia, haemolysis could be the consequence of immune-mediated mechanisms (e.g. *Mycoplasma pneumoniae* and cold agglutinins), not observed in this experience.

We point out the importance of prospective studies on a larger number of patients to better evaluate the impact of SARS-CoV-2 and its treatments on transfusion requirement, taking into account the COVID-19 local epidemiology and the outbreak spread in different regions and countries.

AUTHOR CONTRIBUTIONS

Study design: ULR, GG, SC. Clinical management of patients: FM, MP, FP. Data Collection: GG, MF. Data analysis and interpretation: ULR, GG, SC. Drafting of manuscript: ULR. Critical revision of manuscript: AA, SC. All Authors interpreted the data analysis, read and approved the final draft.

CONFLICT OF INTEREST

The authors have no competing interests.

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