

leukaemia (R/R AML) results were encouraging: 78.6% of the overall response rate (ORR) (manuscript in preparation) without infusion-related toxicity. In this study, we saw unexpected favourable activity in subgroups of patients with central nervous system (CNS) leukaemia and with severe infection; in two of the latter, unsuspected pulmonary tuberculosis and aspergillosis were diagnosed as a NK cell infusion-emergent effect, with no hypoxia, and symptoms subsiding days after emergence.¹⁴ In fact, none of our 14 DB-NK cell adoptive immunotherapies caused hypoxia, neither during DB-NK cell infusions nor later in their clinical course.

RNA analysis of expanded DB-NK cells utilizing our manufacturing platform revealed the absence of ACE-2 receptor (Dean A. Lee, personal communication).

Lessons learned from the passive transfer of antibodies with convalescent plasma to treat infectious diseases indicate better results when the transfer is done earlier in the course of the disease. Convalescent plasma appears effective for SAR-CoV-2; however, it is becoming clear that severe patients already in the overwhelming cytokine storm and coagulopathy phase are less prone to have a benefit.¹⁵

Since the idea is to establish an adaptive immune response as early as possible, and to that end, to attempt to overcome lung immune suppression by infusing highly activated DB-NK cells, it is our belief that NK cells should be infused early in the course of the disease since time to develop a robust immune adaptive response is the key point of the proposed therapy.

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Transfusion demand in COVID-19 patients from the Korean population: a nationwide study in South Korea

As patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) often present coagulopathy depending on disease severity, appropriate prevention and treatment for haemodynamics control are most essential for coronavirus disease 2019 (COVID-19) management.¹

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Although several papers warned that, as expected, there was a decrease in the number of blood donations in the COVID-19 pandemic,^{2,3} few studies investigated the actual prevalence of blood transfusions requested in hospitalized COVID-19 patients,^{4,5} and no publication has reported nationwide

Table I. Demographic and clinical characteristics of Korean COVID-19 patients.

Characteristics	TotalNo.	Transfusion during COVID-19 treatment period		P value
		YesNo. (%)	NoNo. (%)	
Total number	7 512	93 (1.2)	7 419 (98.8)	
Transfusion product*				
Red blood cell		88 (94.6)		
Platelet concentrate		28 (30.1)		
Fresh frozen plasma		18 (19.4)		
Cryoprecipitate		4 (4.3)		
Age, mean (standard deviation), years	46	68.2 (13.2)	45.7 (19.7)	
Sex				
Men	3 055	49 (52.7)	3 006 (40.5)	0.019
Women	4 457	44 (47.3)	4 413 (59.5)	
Insurance type				
National Health Insurance	6 888	79 (84.9)	6 809 (91.8)	0.029
Medical aids	624	14 (15.1)	610 (8.2)	
Charlson Comorbidity Index				
0	3 709	13 (14.0)	3 696 (49.8)	<.001
1	1 591	12 (12.9)	1 579 (21.3)	
2	635	13 (14.0)	622 (8.4)	
3+	1 577	55 (59.1)	1 522 (20.5)	
Outcome parameters				
ICU admission	914	73 (78.5)	841 (11.3)	<.001
Ventilator usage	121	55 (59.1)	66 (0.9)	<.001
Oxygen therapy	905	76 (81.7)	829 (11.2)	<.001
All-cause mortality	227	45 (48.4)	182 (2.5)	<.001
Associated medical history within five years				
Anticoagulant medication	278	18 (19.4)	260 (3.5)	<.001
Transfusion history	167	20 (21.5)	147 (2.0)	<.001

COVID-19, coronavirus disease 2019; ICU, intensive care unit.

*Patients may have received more than one kind of transfusion product.

results yet. Here, we examined the transfusion demand in COVID-19 patients using the Korean nationwide COVID-19 patient database generated by the government.

The Ministry of Health and Welfare of Korea and the Health Insurance Review and Assessment (HIRA) Service of Korea have jointly released the de-identified nationwide COVID-19 patient data using the Korean National Health Insurance System.⁶ This database contains all claim records (including a five-year period before hospitalization) for 7 512 individuals who were confirmed for COVID-19 and for whom hospitals issued claims to the HIRA until 15 May 2020. Confirmed COVID-19 cases were identified following the Korean Classification of Diseases seventh revision (KCD-7) code, which is a modified version of the tenth revision of the International Classification of Diseases (ICD-10). We identified all the transfusion procedures performed for COVID-19 patients before and during the treatment periods. The procedure codes for transfusion practices included all types of transfusion products based on KCD-7 codes (from X1001 to X2516). Additionally, we divided transfusion events into four subgroups according to transfusion products; red

blood cell (RBC), platelet concentrate (PC), fresh-frozen plasma (FFP), and cryoprecipitate. As the database includes detailed information regarding demographic characteristics, diagnoses, prescriptions, procedures, and patient outcomes, we extracted data for associated risk factors and clinical outcome parameters for COVID-19 patients. For associated risk factors, age, gender, insurance type, comorbidities, and anticoagulant medication history were considered. Comorbidities were defined on the basis of claim codes within one year before the index date and evaluated on the basis of the Charlson Comorbidity Index.⁷ Four clinical outcome parameters during the COVID-19 treatment periods assessed in this study were intensive care unit (ICU) admission, ventilator usage, oxygen therapy, and all-cause mortality. The study protocol for analysis of de-identified patient data was exempted from review by the Institutional Review Board of National Health Insurance Service Ilsan Hospital (NHIMC 2020-04-029).

The proportions of associated risk factors and clinical outcome parameters in the COVID-19 patient group who required blood transfusion therapy were compared with those not receiving any transfusion using Student's *t*-test or

the chi-squared test. Multivariate logistic regression models were used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for all-cause mortality according to transfusion therapy after adjustment of other factors. All tests were two-tailed and differences were considered statistically significant at P values of <0.05 . All statistical analyses were performed using SAS software (version 9.4; SAS Institute, Cary, NC, USA).

Interestingly, 1.2% of all patients ($n = 93$) required blood transfusion during COVID-19 treatment periods (Table 1). While the proportion of RBC transfusion was predominant ($n = 88$), PC and FFP transfusion were also observed ($n = 28$ and $n = 18$, respectively) with 30 patients receiving multiple types of transfusion product. The median amounts of RBC, PC, FFP, and cryoprecipitate received in the transfusion group during COVID-19 treatment periods were 3, 11, 4, and 27 units, respectively.

When anticoagulant medication and transfusion history before the COVID-19 diagnosis were investigated for the transfusion group, 70% of patients who required transfusion ($n = 65$) did not have any history of transfusion or anticoagulant therapy in the preceding five years, suggesting that in the majority of patients who required transfusion during treatment periods unstable haemodynamics was independently caused by COVID-19 itself.

Furthermore, multivariable logistic regression analysis revealed that the all-cause mortality rate was statistically significantly increased in the patients who received transfusion therapy during COVID-19 management after adjusting for age, sex, insurance type, Charlson Comorbidity Index, ICU admission, ventilator usage and oxygen therapy (adjusted OR 1.94; 95% CI 1.02–3.70; P value <0.05).

Taken together, the actual proportion of patients requiring transfusion therapy is 1.2%, which is reassuring in that no extreme additional blood requirement for transfusion is expected due to a dramatic increase in COVID-19 patients who might present unstable haemodynamics. Our results support the previous findings of a recent study by Doyle et al. reporting that blood component usage due to COVID-19 remains low.⁵ As this study represents nationwide results rather than an analysis of hospitalized patients, blood demand in the entire COVID-19 patient population, ranging from asymptomatic individuals to patients with severe symptoms, presented lower requirements of transfusion practice. A recent study by Berzuini et al. revealed greater transfusion requirements in COVID-19 patients with direct antiglobulin test (DAT) positivity compared to those with DAT-negative results.⁴ Although the authors suggested autoimmune haemolytic anaemia as the major underlying pathomechanism for RBC transfusion, our results indicate that the transfusion demand for RBC is higher than those for other blood components possibly due to anaemia during the COVID-19 treatment period.

Coagulopathy is another haematological problem frequently reported in COVID-19 patients.⁸ While high rates of

venous thrombosis and disseminated intravascular coagulation are considered as risk factors for COVID-19 severity,⁹ a recent study by Capecchi et al. reported acquired thrombotic thrombocytopenic purpura associated with COVID-19.¹⁰ In line with the previous study, our results revealed that PC and cryoprecipitate demand was less than 35% among COVID-19 patients who received transfusion. Anticoagulant medication prescribed before COVID-19 diagnosis also did not result in either less mortality or lower transfusion demand in our study.

Furthermore, there is enough evidence supporting that a poor prognosis is associated with blood transfusion during COVID-19 treatment independent of previously known risk factors. Although COVID-19 infection status itself might naturally cause haemodynamic changes, severe imbalances requiring transfusion therapy are not observed remarkably more prevalently when compared with other infections.^{11,12} As our Korean nationwide results might represent real-world transfusion demand in countries with similar strict strategies for early detection of SARS-CoV-2 infection, more studies from countries with higher mortality and infection rates are urgently required.

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Author contributions

JHR and JY designed the study. SAL performed statistical research. JHR performed data analysis. JHR, SAL, CHH, and JY wrote the manuscript. JY supervised the study.

Conflicts of interest

The authors declare to have no potential conflicts of interest regarding the present work.

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Autoimmune haemolytic anaemia and a marked rise in the lymphocyte count associated with COVID-19 in a patient with treatment-naïve chronic lymphocytic leukaemia: a case report

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the causative agent of coronavirus disease 2019 (COVID-19), infects human cells through binding of its S protein to the angiotensin-converting enzyme 2 (ACE-2) receptors on their surface.¹ Given the expression of the later in various organs, COVID-19 has a wide spectrum of clinical presentations, albeit remains mainly a respiratory disease because of the high expression of ACE-2 receptors on type 2 pneumocytes. In addition to the direct cytopathic effect of SARS-CoV-2, dysregulated immune responses are pivotal in the pathogenesis of COVID-19. Furthermore, secondary autoimmune phenomena outside the respiratory system, including autoimmune haemolytic anaemia (AIHA), have been increasingly reported.²

Chronic lymphocytic leukaemia (CLL) is characterised by clonal proliferation and accumulation of mature B cells in the blood, bone marrow (BM), spleen and lymph nodes (LNs). It is the most common type of leukaemia in Western countries with peak incidence in the sixth and seventh decades of life.³ Autoimmune cytopenias are well recognised with CLL, with a 7% incidence quoted for AIHA.⁴ Herein, we report the case of a patient with CLL who developed AIHA, mostly secondary to a cold agglutinin, and a marked increase in lymphocyte count, in the context of worsening COVID-19.

An 80-year-old woman known to have treatment naïve Binet stage A CLL, with 13q deletion, presented to Accident

and Emergency with 5 days history of productive cough, shortness of breath (SOB) and fever warranting admission for suspicion of COVID-19, which was later confirmed by reverse transcriptase-polymerase chain reaction on a nasopharyngeal swab. Other significant comorbidities included congestive cardiac failure and atrial fibrillation, for which she had a dual lead pacemaker *in situ*.

Admission plain chest radiograph (CXR) showed bi-basal consolidation and cardiomegaly (Fig 1), and the full blood count showed a haemoglobin (Hb) level of 134 g/l and a lymphocyte count of $18.6 \times 10^9/l$. Worsening SOB and confusion ensued on day (D) 7 of admission, and a repeat CXR showed worsening of the bilateral peripheral airspace opacities and interstitial shadowing (Fig 1). Concomitantly, the Hb level started to drop, with a nadir of 77 g/l on D 17. Other investigations included a reticulocyte count of 10.6% (0.45–2.42), lactate dehydrogenase (LDH) of 548 iu/l (135–214), and a bilirubin of 47 $\mu\text{mol/l}$ (0–21), which was mainly unconjugated. A direct anti-globulin test was positive (3+) for C3d and negative for immunoglobulin G (IgG), and a blood film showed red cell agglutination, alongside the known CLL (Fig 1). Serology for *Mycoplasma pneumoniae* was negative. Based on these investigations AIHA, mostly secondary to a cold agglutinin, was diagnosed and the patient was managed conservatively and did not require blood product support. Her respiratory illness was managed with intravenous (IV) doxycycline and supplemental oxygen