

## Effect of SARS-CoV-2 Entry Factors on Myeloid Cancers

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**Background:** Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel, highly pathogenic coronavirus that has spread rapidly worldwide and caused an international public health emergency. Patients with hematological cancers are regarded as a high-risk group for coronavirus disease 2019 (COVID-19). However, few reports have investigated factors that might account for the differential severity of COVID-19 disease in these patients.

**Methods:** Gene expression of SARS-CoV-2 entry-promoting factors and entry-restricting factors and the associated effects on myeloid malignancies were evaluated. Gene expression levels of 11 SARS-CoV-2 entry-promoting factors and 4 SARS-CoV-2 entry-restricting factors were analyzed in patients with myelodysplastic syndromes (MDS), chronic myeloid leukemia (CML), and acute myeloid leukemia and its subtypes.

**Results:** Expression levels of promoting and restricting factors were most affected in MDS. Specifically, 4 of the 11 analyzed SARS-CoV-2 entry-promoting factors were significantly increased (TMPRSS4, CD 209, CLEC4G, and CTSB), and 2 of the 4 analyzed SARS-CoV-2 entry-restricting factors were significantly decreased (IFITM1 and IFITM2) in MDS. Patients with CML also exhibited a pattern of significant changes in SARS-CoV-2 entry-promoting and entry-restricting factors. Five of the 11 analyzed SARS-CoV-2 entry-promoting factors were significantly increased (ACE2, TMPRSS2, TMPRSS4, ANPEP, CD209), and 1 of the 4 analyzed SARS-CoV-2 entry-restricting factors was significantly decreased (LY6E) in CML.

**Conclusions:** The present and past results highlight the importance of investigating SARS-CoV-2 entry-promoting factors and entry-restricting factors, because of their crucial role in determining the differential severity of COVID-19 disease. (J Nippon Med Sch 2022; 89: 95–101)

**Key words:** hematological cancers, myeloid cancers, COVID-19, coronavirus entry-promoting factors, coronavirus entry-restricting factors

### Introduction

The emergence of a novel, highly pathogenic coronavirus-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-and its rapid spread globally have resulted in an international public health emergency<sup>1</sup>. Patients infected by SARS-CoV-2, which causes coronavirus disease 2019 (COVID-19) and has a reported mortality rate up to 11%, experience a range of symptoms, including dry cough, fever, headache, dyspnea, and pneumonia, which are similar to those caused by the pathogenic SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV)<sup>2</sup>. There is evidence that SARS-CoV-2

infection can damage multiple organ systems, including the lungs, heart, gastrointestinal tract, kidney, and liver<sup>3</sup>. It is still unknown what causes the wide range of clinical phenotypes observed in those infected with SARS-CoV-2.

It has been reported that cancer patients are at high risk of severe COVID-19 illness because of long-lasting immunodeficiency, receipt of anticancer treatments, and the consequences of treatment procedures (e.g., hematopoietic stem cell transplantation)<sup>4</sup>. These risk factors also apply to patients with hematological malignancies, including myeloid malignancies such as acute myeloid leukemias (AML), chronic myeloid leukemia (CML), and

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Table 1 Number of samples for each myeloid subtype

Myeloid cancer type	Number of Samples
Normal Bone Marrow	74
AML normal karyotype	351
AML inv (16)	28
AML t (8, 21)	40
AML t (15, 17)	37
AML complex	48
AML MLL	38
MDS	206
CML	76
Total	898

myelodysplastic syndromes (MDS). Despite this general assumption that cancer is a factor associated with a high risk for severe COVID-19 illness, a recent meta-analysis study found that, among pre-existing comorbidities, cancer accounted for only 1.4% of deaths from COVID-19<sup>5</sup>. Further studies are needed to identify additional factors that might account for the differential severity of COVID-19 disease.

It remains unclear whether severe COVID-19 illnesses are caused by direct infection of the affected organs, indirect effects mediated by comorbidities, or both. To answer this question, we need a better understanding of which malignancies are associated with upregulation of factors favorable to SARS-CoV-2 infection or downregulation of factors that restrict SARS-CoV-2 infection. For example, several studies reported that patients with hematological malignancies and COVID-19 are at high risk of death regardless of disease phase or treatment status<sup>6,7</sup>. Therefore, this study aimed to examine expression levels of factors that promote SARS-CoV-2 entry, as well as factors that restrict SARS-CoV-2 entry, in patients with myeloid malignancies and to provide a molecular stratification that could be used to predict patient outcomes as the pandemic continues and evolves.

## Materials and Methods

### Datasets

The gene expression data used in this study were extracted from the Microarray Innovations in Leukemia (MILE) study under accession number GSE13159<sup>8</sup>. The MILE study was designed to assess the clinical accuracy of gene expression profiles and compare it to that of standard leukemia laboratory methods for acute and chronic leukemia subclasses. In this study, gene expression data were extracted for MDS, AML, CML, and a

control group (i.e., normal bone marrow). All samples were obtained from untreated patients at the time of diagnosis. Cells used for microarray analysis were collected from the purified fraction of mononuclear cells after Ficoll density centrifugation<sup>8</sup>. **Table 1** shows the number of samples that were used in this study for each myeloid subtype. It is important to highlight that a batch effect was applied to these experiments.

### Selection of Candidate Genes

The candidate genes that promote SARS-CoV-2 entry and those that restrict SARS-CoV-2 entry were carefully selected on the basis of the results of a study that mapped human coronavirus entry factors by using single-cell transcriptome profiling<sup>9</sup>. The total list was narrowed down to 28 human genes that were curated and referred to as SARS-CoV-2- and coronavirus-associated receptors and factors. For the purpose of this study, an additional exclusion step was performed to eliminate factors that were not the focus of this study (i.e., its main role was after the infection occurred). Specifically, factors required for virus genome replication, virus trafficking or assembly, and interaction with SARS-CoV-2 proteins were excluded. As a result, this study investigated gene expression of 15 genes, of which 11 candidates are considered SARS-CoV-2 entry-promoting factors and 4 are considered SARS-CoV-2 entry-restricting factors. The mRNA expression data for the selected genes/factors were compiled from the publicly available website BloodSpot by using the option Max probe to ensure use of the probe with the highest intensity within each population (<http://www.bloodspot.eu>)<sup>10</sup>.

### Statistical Analysis

All statistical analyses were performed using Student's *t* test (unpaired, two-tailed) with SPSS software (v20). Differences were considered non-significant at  $p \geq 0.05$  or statistically significant, with \* (1 star) representing  $p < 0.05$ , \*\* (2 stars) representing  $p < 0.01$ , and \*\*\* (3 stars) representing  $p < 0.001$ .

## Results

This investigation of the expression levels of candidates that promote SARS-CoV-2 and those that restrict SARS-CoV-2 entry was performed based on the gene list recently published by Sing et al<sup>9</sup>. Of the 28 human genes that were curated and referred to as SARS-CoV-2- and coronavirus-associated receptors and factors, 11 candidates that promote SARS-CoV-2 entry and 4 candidates that restrict SARS-CoV-2 entry were selected (**Table 2**).

Table 2 Characteristics of the selected genes used in this study

Category	Gene name	Gene full name	Other name (s)
SARS-CoV-2 entry promoting genes	ACE2	Angiotensin I Converting Enzyme 2	ACEH
	TMPRSS2	Transmembrane Serine Protease 2	Epitheliasin
	TMPRSS4	Transmembrane Serine Protease 4	CAPH2
	BSG	Basigin	CD147, BASIGIN
	ANPEP	Alanyl Aminopeptidase	CD13, APN, Gp150
	CD209	CD209 Molecule	DC-SIGN, CLEC4 L
	CLEC4G	C-Type Lectin Domain Family 4 Member G	LSECTin, DTTR431
	CLEC4M	C-Type Lectin Domain Family 4 Member M	DC-SIGNR, LSIGN, CD299, CD209 L
	DPP4	Dipeptidyl Peptidase 4	CD26, ADABP, ADCP2
	Furin	Paired Basic Amino Acid Cleaving Enzyme	PACE, PCSK3, SPC1
CTSB	Cathepsin B	APPS, CPSB	
SARS-CoV-2 entry restricting genes	IFITM1	Interferon Induced Transmembrane Protein 1	CD225, IFI17, DSPA2a
	IFITM2	Interferon Induced Transmembrane Protein 2	DSPA2c
	IFITM3	Interferon Induced Transmembrane Protein 3	DSPA2b, IP15
	LY6E	Lymphocyte Antigen 6 Family Member E	RIGE, SCA2

### Expression Levels of Candidates That Promote SARS-CoV-2 Entry in Myeloid Cancers

First, 2 well-studied genes were analyzed: angiotensin-converting enzyme 2 (ACE2), which has been identified as a prime receptor, and transmembrane serine protease 2 (TMPRSS2), which has been identified as a critical protease for cell entry<sup>11</sup>. As shown in **Figure 1A** and **Figure 1B**, the expression level of ACE2 was significantly increased in CML, while the expression level of TMPRSS2 was significantly increased in CML, AML MLL, and AML complex. The expression level of TMPRSS4, another cellular protease recently shown to be capable of functioning as an alternative priming factor for SARS-CoV-2 in human cells<sup>12</sup>, was significantly increased in MDS and CML (**Fig. 1C**). The expression level of BSG, another confirmed receptor for SARS-CoV-2<sup>13</sup>, was not significantly increased in any type of myeloid cancer (**Fig. 1D**).

Next, the analysis focused on expression levels of receptors that were confirmed experimentally to facilitate entry of SARS-CoV or MERS-CoV—that is, candidates that promote SARS-CoV-2 entry<sup>14</sup>. These receptors include ANPEP, CD209, CLEC4G, CLEC4M, and DPP4. As shown in **Figure 1E**, the expression level of ANPEP was significantly increased in AML inv (16) and CML. The expression level of CD209 was significantly increased in AML complex, MDS, and CML (**Fig. 1F**), and the expression level of CLEC4G was significantly increased in AML MLL and MDS (**Fig. 1G**). Expression levels of CLEC4M and DPP4 were not significantly increased in

any type of myeloid cancer (**Fig. 1H** and **Fig. 1I** respectively). Next, 2 other proteases that possibly mediate human SARS-CoV-2 entry, furin and CTSB<sup>15</sup>, were examined. The expression level of furin was significantly increased in AML with a normal karyotype (AML NK) and AML complex (**Fig. 1J**), and the expression level of CTSB was significantly increased only in MDS (**Fig. 1K**).

### Expression Levels of Candidates That Restrict SARS-CoV-2 Entry in Myeloid Cancers

Theoretically, a decrease in restricting factors can be as important as an increase in promoting factors, because it represents a breach in the defense against the virus and might allow its entry. Therefore, the analysis then focused on 4 restriction factors that are known to protect cells against the entry of a broad range of enveloped RNA viruses, including SARS-CoV (i.e., IFITM1, IFITM2, and IFITM3<sup>16</sup>) or against the entry of SARS-CoV-2 (i.e., LY6E<sup>17</sup>). As shown in **Figure 2A**, the IFITM1 expression level was significantly downregulated in 7 of the 8 investigated myeloid cancers. A similar pattern was observed when the IFITM2 expression level was analyzed, as its expression was significantly downregulated in 6 of the 8 investigated myeloid cancers (**Fig. 2B**). For IFITM3 and LY6E, the expression level was significantly downregulated in 2 and in 1 of the 8 investigated myeloid cancers, respectively (**Fig. 2C** and **Fig. 2D**).

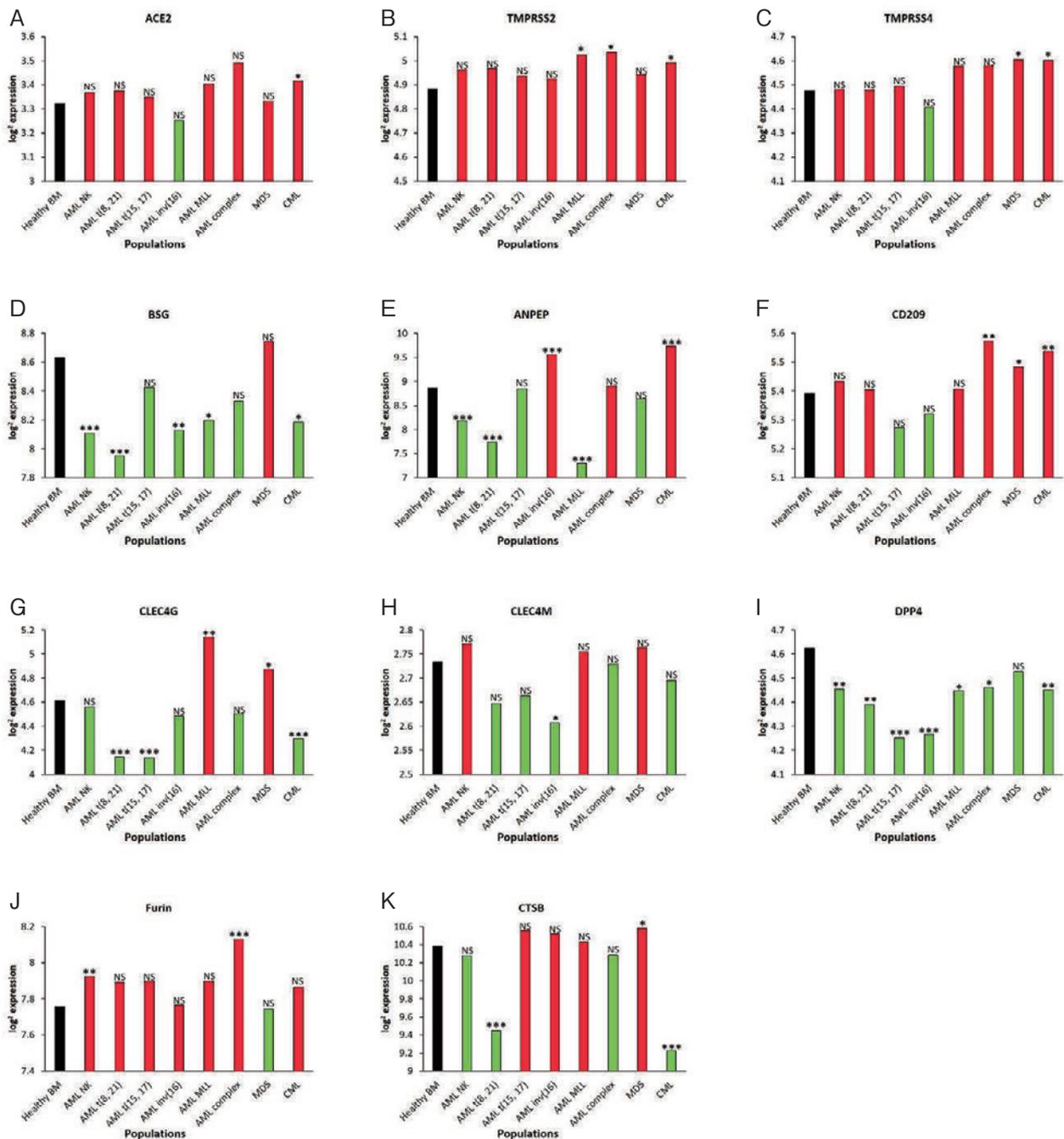


Fig. 1 Expression levels of 11 SARS-CoV-2 entry-promoting factors in myeloid cancers.

Gene expression data mined from Bloodspot showing gene expression levels in patients with myeloid cancer relative to those in normal bone marrow (A, ACE2; B, TMPRSS2; C, TMPRSS4; D, BSG; E, ANPEP; F, CD209; G, CLEC4G; H, CLEC4M; I, DPP4; J, Furin; K, CTSB). Max probe was used for all genes. NS indicates non-significant ( $p \geq 0.05$ ), \* (one star) indicates  $p < 0.05$ , \*\* (two stars) indicates  $p < 0.01$ , and \*\*\* (three stars) indicates  $p < 0.001$ . Healthy BM: healthy bone marrow, AML NK: acute myeloid leukemia normal karyotype, MDS: myelodysplastic syndrome, and CML: chronic myelogenous leukemia.

### Risk Stratification for Myeloid Cancers in Relation to Expression Levels of SARS-CoV-2 Entry-Promoting and Entry-Restricting Factors

The next stage of the investigation focused on the main question of this study: whether the severity of COVID-19 can be predicted by expression levels of SARS-CoV-2 entry-promoting and entry-restricting factors. First,

myeloid cancers that have significantly increased expression of SARS-CoV-2 entry-promoting factors or significantly decreased expression of SARS-CoV-2 entry-restricting factors were ranked. As shown in **Table 3**, expression levels of promoting and restricting factors were most affected in MDS and CML. Specifically, 4 of the 11 analyzed SARS-CoV-2 entry-promoting factors were sig-

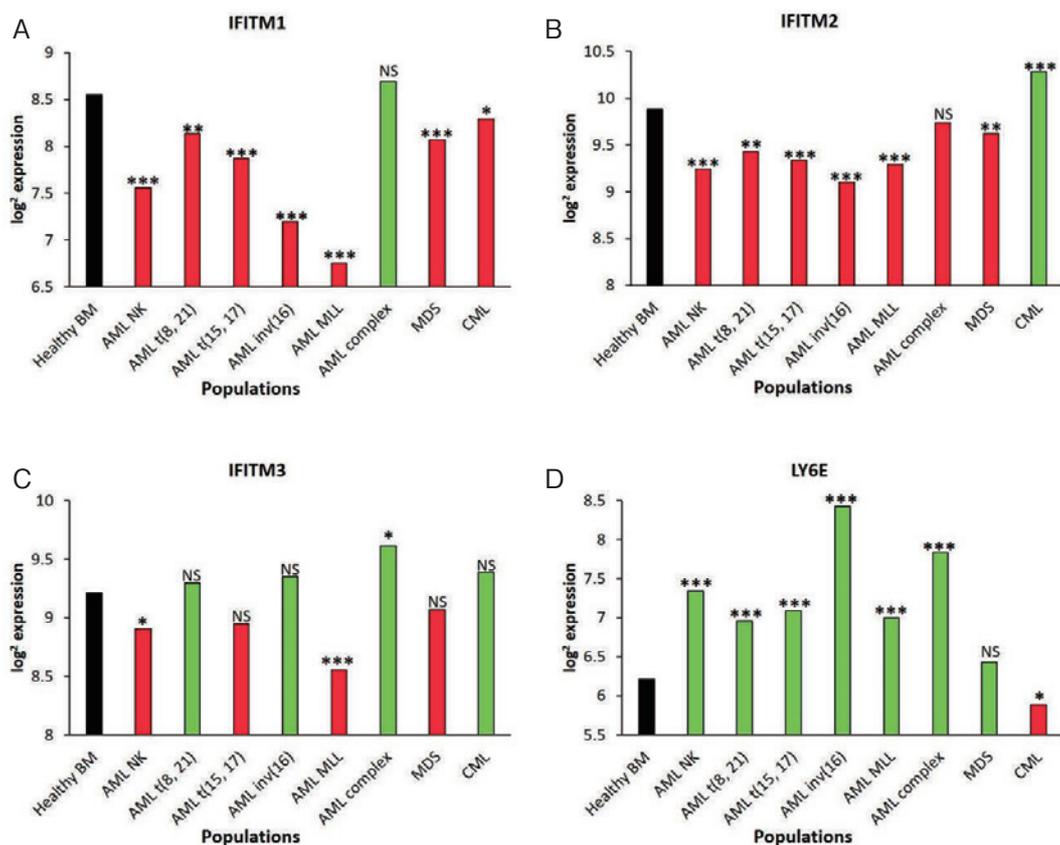


Fig. 2 Expression levels of 4 SARS-CoV-2 entry-restricting factors in myeloid cancers. Gene expression data mined from Bloodspot showing gene expression levels in patients with myeloid cancer relative to those in normal bone marrow (A, IFITM1; B, IFITM2; C, IFITM3; D, LY6E). Max probe was used for all genes. NS indicates non-significant ( $p \geq 0.05$ ), \* (one star) indicates  $p < 0.05$ , \*\* (two stars) indicates  $p < 0.01$ , and \*\*\* (three stars) indicates  $p < 0.001$ . Healthy BM: healthy bone marrow, AML NK: acute myeloid leukemia normal karyotype, MDS: myelodysplastic syndrome, and CML: chronic myelogenous leukemia.

Table 3 List of myeloid cancers and their respective promoting and/or restricting factors associated with significant changes

Myeloid cancer type	Number of significantly increased SARS-CoV-2 entry-promoting factors	Number of significantly decreased SARS-CoV-2 entry-restricting factors
MDS	4 (TMPRSS4, CD209, CLEC4G, CTSB)	2 (IFITM1, IFITM2)
CML	5 (ACE2, TMPRSS2, TMPRSS4, ANPEP, CD209)	1 (LY6E)
AML MLL	2 (TMPRSS2, CLEC4G)	3 (IFITM1, IFITM2, IFITM3)
AML NK	1 (Furin)	3 (IFITM1, IFITM2, IFITM3)
AML complex	3 (TMPRSS2, CD209, Furin)	0
AML inv (16)	1 (ANPEP)	2 (IFITM1, IFITM2)
AML t (8, 21)	0	2 (IFITM1, IFITM2)
AML t (15, 17)	0	2 (IFITM1, IFITM2)

nificantly increased (i.e., TMPRSS4, CD209, CLEC4G, and CTSB), and 2 of the 4 analyzed SARS-CoV-2 entry-restricting factors were significantly decreased (i.e., IFITM1 and IFITM2) in MDS. Similarly, 5 of the 11 ana-

lyzed SARS-CoV-2 entry-promoting factors were significantly increased (i.e., ACE2, TMPRSS2, TMPRSS4, ANPEP, CD209), and 1 of the 4 analyzed SARS-CoV-2 entry-restricting factors was significantly decreased (i.e., LY6E)

in CML. AML MLL had significantly increased expression of 2 SARS-CoV-2 entry-promoting factors (i.e., Tmprss2 and Clec4g) and significantly decreased expression of 3 SARS-CoV-2 entry-restricting factors (i.e., Ifitm1, Ifitm2, and Ifitm3). AML NK had significantly decreased expression of these 3 SARS-CoV-2 entry-restricting factors (i.e., Ifitm1, Ifitm2, and Ifitm3) but significantly increased expression of 1 SARS-CoV-2 entry-promoting factor (i.e., furin). AML complex had significantly increased expression of 3 SARS-CoV-2 entry-promoting factors (i.e., Tmprss2, CD209, and furin), while none of the SARS-CoV-2 entry-restricting factors were significantly decreased. Finally, the other AML aberrations-AML inv(16), AML t(8, 21), and AML t(15, 17)-had significantly decreased expression of 2 SARS-CoV-2 entry-restricting factors (i.e., Ifitm1 and Ifitm2).

### Discussion

Identification and characterization of patient risk groups is the most efficient approach to reduce the impact of the COVID-19 pandemic on the health care system. The present results indicate that patients with MDS and CML are at high risk of contracting severe COVID-19 because these diseases promote SARS-CoV-2 entry. These findings highlight the importance of examining different cancer subtypes and including the most updated experimentally proven factors that promote SARS-CoV-2 entry.

Cancers change the expression levels of many proteins in the body. Few studies have investigated expression levels of SARS-CoV-2 entry-promoting candidates or SARS-CoV-2 entry-restricting candidates. Ren et al. found no significant correlation between ACE2 expression and COVID-19 severity in patients with malignant tumors<sup>18</sup>. In the present study, only CML showed a significantly higher expression of ACE2, as compared with that in healthy individuals. Together, these findings indicate that the mechanism of SARS-CoV-2 infection requires cofactors and/or receptors other than ACE2.

A key finding of this study was that, in MDS, the expression of more than one-third of the analyzed SARS-CoV-2 entry-promoting factors was significantly increased and that expression of 50% of the analyzed SARS-CoV-2 entry-restricting factors was significantly decreased. This observation may explain the high mortality rate in patients with MDS and COVID-19. For example, the largest series of patients with hematological malignancies and COVID-19 to date reported that the death rate in patients with MDS who were COVID-19-positive was 49%<sup>19</sup>.

The World Health Organization has confirmed more than 46 million cases of COVID-19 and 1.2 million deaths worldwide as of early November 2020<sup>20</sup>. These data should be sufficient to inspire decisionmakers to make every effort to perform complete diagnostic evaluations in outpatient settings<sup>21</sup>. In other words, patients (especially those at high risk but not those requiring treatment) should remain at home for as long as possible, thereby decreasing visits to outpatient offices and hospitals and thus reducing their risk of exposure to SARS-CoV-2<sup>21</sup>. Fortunately, several studies of the impact of the COVID-19 pandemic on selected hospitals in Latin America found that the health care systems were not substantially affected<sup>22,23</sup>. Although these are encouraging observations, it is likely that as the pandemic evolves, the burden on the health care system will increase and have adverse effects if appropriate measures are not taken, including the identification and characterization of patient risk groups.

The major strength of this study was its coverage of almost all myeloid subtypes. However, the main limitation was the use of a single dataset, although the large sample size of the utilized dataset increases the applicability of these findings. Therefore, the present data indicate that experimental validation in a clinical setting is warranted.

Patients with cancer are at high risk of complications from SARS-CoV-2 infection because of many factors, including their weak immune system. However, it is unclear which types of cancer increase the likelihood of contracting the virus as a result of the upregulation of entry-promoting factors or downregulation of entry-restricting factors. In conclusion, this study evaluated the impact of myeloid malignancies on some of the well-studied SARS-CoV-2 entry-regulating factors. The present findings provide a framework for a possible novel treatment option involving development of small-molecule inhibitors that can be used to disrupt entry factors and SARS-CoV-2.

**Conflict of Interest:** The author declares no potential conflicts of interest.

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