

# Long-term reduction in the incidence of aplastic anemia and immune thrombocytopenia during the COVID-19 pandemic

Although the coronavirus disease 2019 (COVID-19) pandemic has exerted collateral effects on various diseases, little is known about its impact on the incidence of hematologic diseases. This retrospective study evaluated the incidence of hematologic diseases during the COVID-19 pandemic using the Japanese nationwide database. The overall incidence of hematologic diseases decreased temporarily in April-May 2020 during the first COVID-19 wave, but gradually recovered to baseline over 6 months. The decrease was prominent in slowly progressing malignant and premalignant diseases, while rapidly progressive malignant diseases showed no significant decrease. On the other hand, immune thrombocytopenia (ITP) and idiopathic aplastic anemia (AA) showed a sustained decrease over 6 months, unlike other anemic and cytopenic diseases. Particularly, severe ITP and AA cases showed a more significant decrease. These results suggest community-acquired infectious agents as the leading cause of these diseases. During the COVID-19 pandemic, the government has implemented social restrictions aimed at controlling community severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) transmission. Such restrictions have had widespread collateral effects on diseases other than COVID-19, due to changes in both health care system performance and public behavior including canceling or postponing medical visits.<sup>1</sup> During the first COVID-19 wave, the number of diagnoses of various diseases, including cancers and cardiovascular diseases, declined temporarily,<sup>2-4</sup> but returned to the expected levels by the second half of 2020.<sup>2-4</sup> On the other hand, the public have maintained self-restraint behaviors, such as social distancing and wearing masks, to minimize SARS-CoV-2 transmission through person-to-person contact. Accordingly, many common infectious diseases, such as influenza, substantially decreased and remained low throughout 2020.<sup>5</sup> These observations suggest that the extent and duration of the collateral effect may provide insights into disease etiology and related pathogenesis, particularly in association with infection. Hematologic diseases include various conditions ranging from rapidly progressing malignancies to disorders that are often asymptomatic and diagnosed incidentally as well as those triggered by infection. However, little is known about the collateral effect of the COVID-19 pandemic on the incidence of various hematologic diseases. Therefore, we conducted a retrospective study using the Blood Disease Registration managed by the Japanese So-

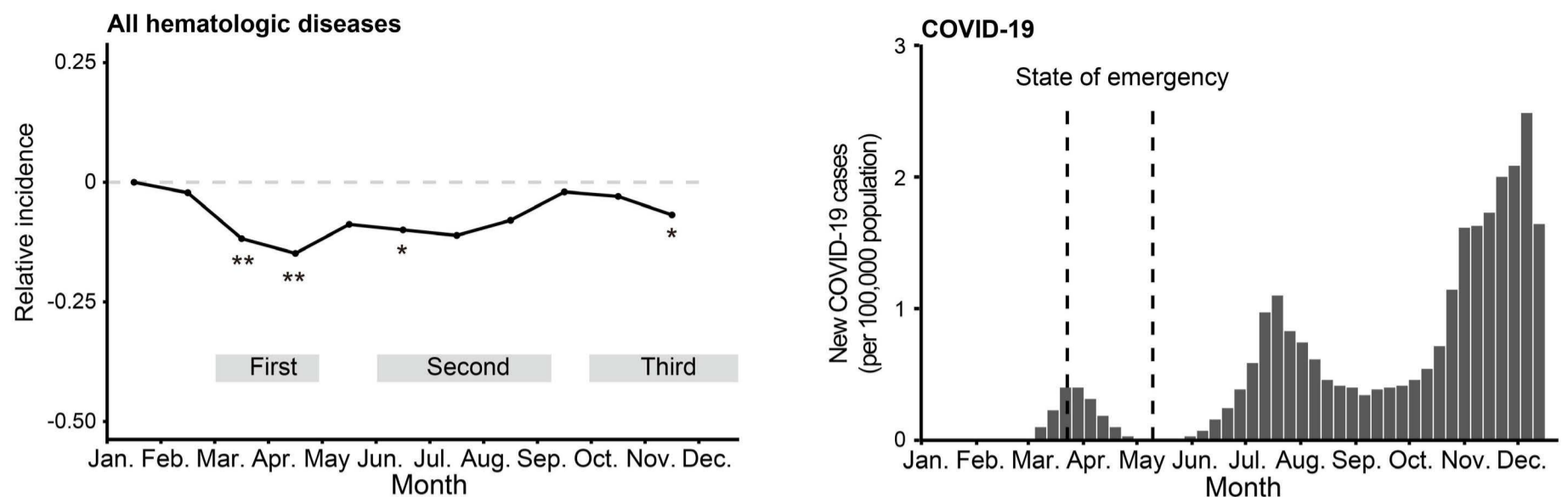
ciety of Hematology (JSH)<sup>6,7</sup> to evaluate the short-term and long-term impact of the COVID-19 pandemic on the number of newly diagnosed hematologic diseases. This study was approved by the committee of academic and statistical investigation of the JSH and the Ethics Committee of Keio University School of Medicine.

The registered diseases consisted of 267 hematologic diseases, and we focused on nine disease categories representing major hematologic diseases: four malignant (acute leukemias, aggressive lymphomas, indolent lymphomas, and plasma cell disorders), three premalignant (myelodysplastic syndromes [MDS], myeloproliferative neoplasms [MPN], and premalignant monoclonal B-cell disorders) and two non-malignant categories (ITP and idiopathic AA) (*Online Supplementary Table S1*).

In order to evaluate the collateral effect of the COVID-19 pandemic, we compared the number of newly diagnosed cases in 2020, when the COVID-19 pandemic began in Japan, with that in 2019. The weekly number of newly diagnosed cases was counted in 4-week segments, and the number in 2020 was corrected by dividing by the ratio of the number of each disease category during January-February in 2020, which was before the COVID-19 pandemic, to that in 2019. The relative incidence was calculated as the difference between the actual number in 2019 and corrected number in 2020 divided by the actual number in 2019, for each disease category per each month, and presented as a 2-month moving average.

We evaluated 85,827 cases, consisting of 43,397 and 42,430 cases diagnosed in 2019 and 2020, respectively. Patient characteristics were similar between 2019 and 2020 (Table 1). The relative incidence for all registered cases and the weekly counts of newly confirmed COVID-19 cases in Japan are shown in Figure 1. There were three COVID-19 waves in 2020 in Japan. During the first wave, when the infection spread and a state of emergency was declared from April to May, the overall incidence of hematologic diseases significantly decreased by 15% ( $P=0.003$ ). During the second and third waves starting from June and October, the overall incidence declined by 10% and 7% ( $P=0.04$  and  $P=0.048$ ), respectively. Therefore, the COVID-19 pandemic influenced the incidence of hematologic diseases, but its extent became smaller over time.

Among malignant diseases, the number of cases diagnosed with acute leukemias, aggressive lymphomas, and plasma cell disorders showed a slight but not statistically



**Figure 1. Relative incidence for all registered cases with hematologic diseases and the number of new COVID-19 cases in Japan.**

Two-month moving average of the decrease rate for all registered cases with hematologic diseases in 2020 compared to 2019 is shown on the left, together with the weekly counts of newly confirmed COVID-19 cases per 100,000 population in 2020 in Japan<sup>13</sup> on the right. Gray boxes indicate the first, second, and third waves of COVID-19, respectively. Vertical dotted lines in the right panel indicate the duration of a state of emergency: it was declared by the Japanese government for Tokyo, Osaka, Kanagawa, Saitama, Chiba, Hyogo, and Fukuoka on April 7 2020, and for remaining prefectures on April 16. It was terminated for all prefectures except Hokkaido, Saitama, Chiba, Tokyo, Kanagawa, Kyoto, Osaka, and Hyogo on May 14, for Kyoto, Osaka, and Hyogo on May 21 and for Hokkaido, Saitama, Chiba, Tokyo, and Kanagawa on May 25. Two-tailed Student's *t*-test was used to compare the actual weekly numbers in 2019 and the corrected weekly numbers in 2020 for 2 months. \**P*<0.05; \*\**P*< 0.01.

**Table 1.** Patient demographics.

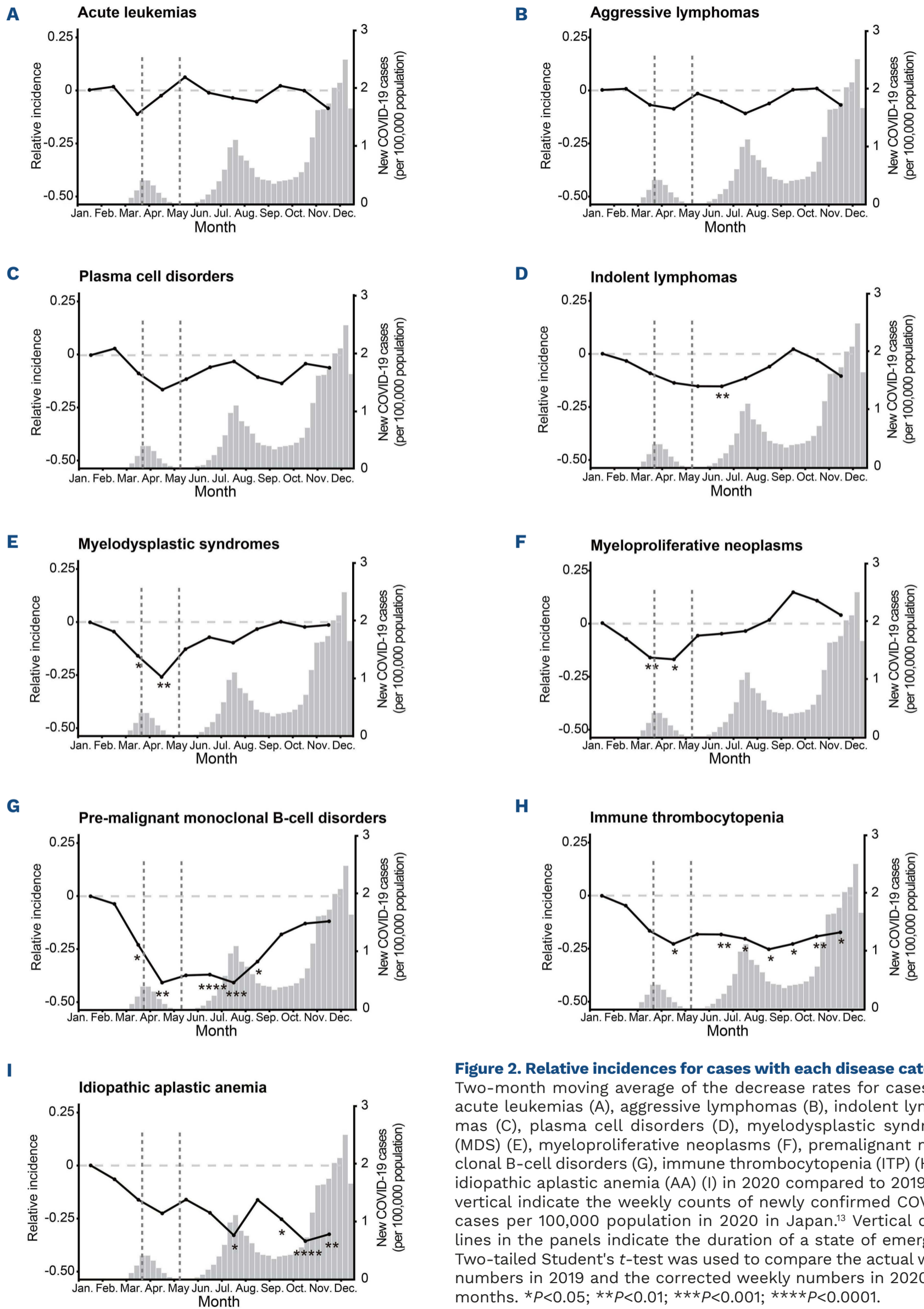
Year of diagnosis	Total (N=85,827)	2019 (N=43,397)	2020 (N=42,430)	<i>P</i>
N of institutions	410	410	401	
Median age in years (range)	71 (0-103)	71 (0-103)	71 (0-101)	0.17
Male sex, N (%)	48,011 (56)	24,148 (56)	23,863 (56)	0.08
Disease categories, N (%)				
Acute leukemias	8,348 (10)	4,164 (10)	4,184 (10)	
Aggressive lymphomas	22,380 (26)	11,089 (26)	11,291 (27)	
Indolent lymphomas	11,546 (14)	5,832 (13)	5,714 (14)	
Plasma cell disorders	6,788 (8)	3,449 (8)	3,339 (8)	
Myelodysplastic syndromes	8,309 (10)	4,263 (10)	4,046 (10)	
Myeloproliferative neoplasms	8,949 (10)	4,475 (10)	4,474 (11)	
Pre-malignant monoclonal B-cell disorders	2,914 (3)	1,507 (3)	1,407 (3)	
Immune thrombocytopenia	5,191 (6)	2,706 (6)	2,485 (6)	
Idiopathic aplastic anemia	1,473 (2)	780 (2)	693 (2)	

Comparisons between groups were based on the Wilcoxon rank-sum test for continuous data, and the Fisher's exact test for categorical data.

significant decrease by at most 16% during the three COVID-19 waves (Figure 2A, B and D). In contrast, the number of cases with indolent lymphomas slowly decreased and reached a significantly lower level of 15% (*P*=0.007) in June-July, and gradually recovered to the baseline level (Figure 2C).

In premalignant diseases, the number of MDS and MPN cases significantly dropped by 26% and 17% (*P*=0.001 and *P*=0.03) respectively, in April-May, and these numbers gradually recovered to the baseline level in August-September (Figure 2E, F). Meanwhile, the number of cases with premalignant monoclonal B-cell disorders (mainly consisting of monoclonal gammopathy of unknown sig-

nificance) significantly decreased since March-April, with the largest decline of 41% (*P*=0.003) in April-May among disease categories (Figure 2G). The number continued to be significantly lower for 6 months and gradually recovered to a non-significant level by the end of 2020. Interestingly, the incidence of non-malignant disease showed a different time course: the number of ITP cases rapidly decreased by 23% (*P*=0.02) in April-May, and continued to be significantly lower (17–25% reduction) over 8 months until the end of 2020 (Figure 2H). On the other hand, the number of idiopathic AA cases did not show a statistically significant decline in April-May (Figure 2I). However, it gradually decreased thereafter, with a statis-



**Figure 2. Relative incidences for cases with each disease category.** Two-month moving average of the decrease rates for cases with acute leukemias (A), aggressive lymphomas (B), indolent lymphomas (C), plasma cell disorders (D), myelodysplastic syndromes (MDS) (E), myeloproliferative neoplasms (F), premalignant monoclonal B-cell disorders (G), immune thrombocytopenia (ITP) (H) and idiopathic aplastic anemia (AA) (I) in 2020 compared to 2019. Gray vertical indicate the weekly counts of newly confirmed COVID-19 cases per 100,000 population in 2020 in Japan.<sup>13</sup> Vertical dotted lines in the panels indicate the duration of a state of emergency. Two-tailed Student's *t*-test was used to compare the actual weekly numbers in 2019 and the corrected weekly numbers in 2020 for 2 months. \**P*<0.05; \*\**P*<0.01; \*\*\**P*<0.001; \*\*\*\**P*<0.0001.



tically significant decline in July–August, and further decreased after September–October, reaching 36% in October–November.

Next, we evaluated differences according to disease severity in ITP, idiopathic AA and MDS, which show similar symptoms and laboratory findings at diagnosis. In ITP, the decrease rate of mild diseases did not reach statistical significance throughout the year (*Online Supplementary Figure S1A*). In contrast, severe diseases showed a significant decrease of 24% ( $P=0.03$ ) in April–May, remained significantly lower, with a maximum decrease of 37% ( $P=0.004$ ) in August–September, and did not show signs of recovery until the end of 2020. Similarly, in idiopathic AA, mild to moderate diseases showed a sustained decreasing trend of up to 28% in July–August, but which were insignificant throughout the year (*Online Supplementary Figure S1B*). Severe diseases showed a similar decreasing trend of 27% ( $P=0.12$ ) in April–May, continued to decrease after July–August, reached a maximal reduction of 49% ( $P=0.001$ ) in October–November, and did not recover until the end of 2020. On the other hand, in MDS, the low-risk group showed a significant decrease of 32% in April–May during the first wave and recovered rapidly. The high-risk group showed a slight but mostly insignificant decrease during the first and second waves (by at most 15%) and then recovered (*Online Supplementary Figure S1C*). Therefore, the collateral effect is more robust and persistent in severe forms of ITP and idiopathic AA.

Here we comprehensively investigated the changes in the incidences of various hematologic diseases during the COVID-19 pandemic, and revealed that the extent and timing of such collateral effects depend on the nature and aggressiveness of the disease. We revealed that the incidence of ITP and idiopathic AA continued to decline until the end of 2020. Although limited medical access caused under-reporting of disease incidence, particularly during the first wave, this cannot explain the long-term reduction of ITP and idiopathic AA incidences, as other anemic and cytopenic diseases showed a contrasting trend. While the individual etiology is unknown in many cases, it is widely accepted that infection can trigger the development and/or acute exacerbation of ITP.<sup>8,9</sup> Thus, it is reasonable to postulate that reduced person-to-person contact due to social restrictions imposed during the COVID-19 pandemic contribute to the rapid and sustained decrease (by approximately 20%) of ITP incidence especially in severe cases, suggesting a critical role of community-acquired infectious pathogens in ITP pathogenesis regardless of age.

Idiopathic AA also showed distinctive longitudinal changes in incidence, which suggests a crucial role of infectious etiology in AA pathogenesis. Immune destruction is considered the main cause of idiopathic AA, especially when

severe.<sup>10,11</sup> Although AA can present as a rare sequela of certain viral infections, such as Epstein-Barr virus (called acquired or secondary AA), in most cases, no apparent causes are identified, leading to the diagnosis of idiopathic AA.<sup>10,11</sup> However, our results suggest that a substantial proportion (at least one-third) of idiopathic AA, particularly severe one, is caused by infectious pathogens. This unique longitudinal change suggests a possible interval between the triggering infection and the development of AA. This finding supports the pathological hypothesis that viral infection provokes an aberrant immune response, triggering an oligoclonal expansion of cytotoxic T cells that destroy hematopoietic stem cells.<sup>10,12</sup> Given that *Helicobacter pylori* eradication is a standard treatment of ITP<sup>8,9</sup>, identifying such pathogens can lead to the development of novel anti-infective treatments and biomarkers for immunosuppressive therapies against these diseases.

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### Contributions

MS designed the research; analyzed and interpreted the data; and wrote the first draft of the manuscript. YK and KM analyzed and interpreted the data and wrote the first draft of the manuscript. EM interpreted the data and wrote the first draft of the manuscript. KK designed the research; analyzed and interpreted the data; and revised the draft of the manuscript. MS, YK, KM and KK had full access to all data and interpreted and reviewed the data. All authors critically reviewed and approved the manuscript. All authors took final responsibility for the decision to submit for publication.

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### Data-sharing statement

The datasets used in the study can be requested for use in research studies, subject to obtaining necessary permissions from the committee of academic and statistical investigation of the Japanese Society of Hematology.

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