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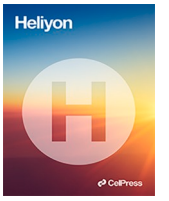

Research article

Cardiovascular events after the initiation of immune checkpoint inhibitors

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ABSTRACT

We sought to clarify the incidence of major adverse cardiac events (MACE) after the initiation of immune checkpoint inhibitors (ICIs). We analyzed the JMDC Claims Database between 2005 and 2021. The study included 2972 patients with no history of cardiovascular disease and a prescription for an ICI. The primary outcome was the incidence of MACE, including myocarditis, pericarditis, Takotsubo cardiomyopathy, atrio-ventricular block, heart failure, myocardial infarction, and stroke. The median age of study participants was 59 (Q1-Q3 53–65) years, and 2163 participants (72.8%) were male. Lung cancer was the most common cancer site (n = 1603). Among ICIs, programmed cell death-1 (PD-1) was most frequently used, and a combination ICI treatment was conducted in 110 patients (3.7%). During a mean follow-up of 358 ± 327 days, 419 MACE events were recorded. The incidence rate of myocarditis, pericarditis, Takotsubo cardiomyopathy, atrio-ventricular block, heart failure, myocardial infarction, and stroke was 3.4, 142.3, 10.3, 17.2, 1191.2, 55.2, and 278.5 per 10,000 person-years, respectively. The incidence of cardiovascular events was higher within 180 days after the initial prescription of ICI. The continuation rate of ICI after MACE was 38.4%. In conclusion, our analysis of a nationwide epidemiological dataset demonstrated the incidence of MACE after the initiation of ICI treatment. The incidence of heart failure was higher than expected, and the continuation rate of ICI treatment after MACE was low. Our results indicated the importance of monitoring and prevention of cardiovascular events in cancer patients requiring ICI treatment.

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1. Introduction

Immune checkpoint inhibitors (ICIs) can lead to immune-related adverse events (irAEs) which could occasionally have fatal consequences [1–5]. Major adverse cardiac events (MACEs) associated with ICIs are uncommon (1%), but they have numerous effects on the cardiovascular system. Myocarditis, congestive heart failure (HF), pericarditis, and arrhythmias are the main components of ICI-MACE, and ICI-MACE may potentially pose a life-threatening situation. For example, fulminant myocarditis which typically occurs within one month after the initiation of ICIs, is reported to be fatal in 25–50% of cases [6–8]. Despite its clinical significance, there have been scarce data on the incidence of ICI-MACE using a large-scale epidemiological dataset. Because patients requiring ICI treatment are those with advanced cancer, accurate assessment of the incidence of cardiovascular complications is practically difficult due to loss of follow-up or transfer of physicians. Japan has a universal health insurance system, and therefore, all medical records or procedures which are conducted under this insurance system are theoretically obtained from administrative claims data. From this point of view, utilizing the insurance database in Japan would be an ideal way to accurately assess the incidence of cardiovascular events following ICI treatment. Herein, we sought to uncover the incidence of cardiovascular disease (CVD) adverse events after the initial prescription of ICIs using the JMDC Claims Database which is a nationwide claims dataset in Japan.

2. Methods

2.1. Study design and population

We performed this retrospective cohort study using the JMDC Claims Database (JMDC Inc., Tokyo, Japan), an administrative claims database, between January 2005 and April 2021 [9–11]. The JMDC Claims Database includes administrative claims data recorded using the International Classification of Diseases, 10th Revision (ICD-10) coding. This database is available for purchase from JMDC Inc. (https://www.jmdc.co.jp/en/). We extracted individuals who were treated using ICIs (nivolumab [WHO-ATC codes: L01XC17], pembrolizumab [WHO-ATC codes: L01XC18], ipilimumab [WHO-ATC codes: L01XC11], durvalumab [WHO-ATC codes: L01XC28], avelumab [WHO-ATC codes: L01XC31], atezolizumab [WHO-ATC codes: L01XC32]). We excluded 851 individuals with prior history of CVD (myocarditis, pericarditis, Takotsubo cardiomyopathy, atrioventricular [AV] block, HF, myocardial infarction [MI], and stroke) based on the ICD-10 codes. Finally, 2972 individuals were analyzed in the present study.

2.2. Ethics

The Ethical Committee of the University of Tokyo approved the present study (number: 2018–10862), which was conducted in accordance with the Declaration of Helsinki. Since all data included in the JMDC Claims Database were anonymized and de-identified, the requirement for informed consent was waived.

2.3. Measurements

From the JMDC Claims data, we obtained the diagnosis of following malignant neoplasms: malignant melanoma (ICD-10 codes: C43), lung cancer (ICD-10 codes: C34), renal cell cancer (ICD-10 codes: C64), Hodgkin lymphoma (ICD-10 codes: C81), head and neck cancer (ICD-10 codes: C00–13, C30–33, C432, and C442), stomach cancer (ICD-10 codes: C16), esophagus cancer (ICD-10 codes: C15), colorectal cancer (ICD-10 codes: C18-20), urothelial cancer (ICD-10 codes: C65-68), malignant neoplasm without specification of site (ICD-10 codes: C80), Merkel cell carcinoma (ICD-10 codes: C44), breast cancer (ICD-10 codes: C50), liver cancer (ICD-10 codes: C22), and corpus uteri cancer (ICD-10 codes: C54). ICIs were approved for the treatment of these malignant neoplasms in the Japanese healthcare setting. Furthermore, we collected data on blood pressure-, glucose-, and lipid-lowering medications according to the WHO-ATC codes.

2.4. Outcomes

The primary outcome was the incidence of MACEs, including myocarditis (ICD-10 codes: I40-41), pericarditis (ICD-10 codes: I30-32), Takotsubo cardiomyopathy (ICD-10 codes: I518), AV block (ICD-10 codes: I44-45), HF (ICD-10 codes: I500, I501, I509, and I110), MI (ICD-10 codes: I210–I214 and I219), and stroke (ICD-10 codes: I630, I631–I636, I638, I639, I600–I611, I613–I616, I619, I629, and G459). The secondary outcome was separately defined as myocarditis, pericarditis, Takotsubo cardiomyopathy, AV block, HF, MI, and stroke. We followed study participants from the date of the initial ICI prescription to death, leaving insurance coverage, or study end date (April 2021).

2.5. Statistical procedure

Clinical characteristics at the prescription date of ICIs were presented as numbers (percentages) or medians (interquartile ranges) as appropriate. We calculated the incidence rate by dividing the number of cases by person-years of follow-up period. The incidence rate of cardiovascular events was presented as per 10,000 person-years. We divided individuals into two groups according to the incident of MACEs. Clinical characteristics at the prescription date of ICIs between the two groups were compared using the chi-square or Wilcoxon rank-sum test. A multivariable Cox proportional hazard regression model was used to examine the predictors of MACE. We

described the prescription rate of diuretics (WHO-ATC codes: C03AA, C03CA, and C03CB), renin-angiotensin system-inhibitors (WHO-ATC codes: C09), and beta-blockers (WHO-ATC codes: C07) in patients developing HF. Statistical significance was set at a p-value <0.05. All statistical analyses were conducted using STATA version 17 (StataCorp LLC, College Station, TX, USA).

3. Results

3.1. Clinical characteristics

Clinical characteristics were presented in Table 1. The median age of study participants was 59 (Q1-Q3 53–65) years, and 2163 participants (72.8%) were male. Lung cancer was the most common cancer site (n = 1603), followed by stomach cancer (n = 469), malignant neoplasm without specification of site (n = 299), head and neck cancer (n = 295), and renal cell cancer (n = 261). Among ICIs, programmed cell death-1 (PD-1) was most frequently used (n = 2274), and a combination ICI treatment was conducted in 110 patients. A total of 581 individuals died during the follow-up period. The loss to follow-up, defined as leaving insurance coverage before April 2021, was observed in 1118 individuals.

3.2. Cardiovascular events

The number and incidence rate of MACE were summarized in Table 2. During a mean follow-up of 358 ± 327 days, 419 MACE events were recorded (1583.9 [1439.2–1743.0] per 10,000 person-years). The incidence rate of myocarditis, pericarditis, Takotsubo cardiomyopathy, AV block, HF, MI, and stroke was 3.4 (0.5–24.4), 142.3 (104.8–193.3), 10.3 (3.3–32.0), 17.2 (7.2–41.4), 1191.2 (1068.0–1328.7), 55.2 (33.8–90.1), 278.5 (223.7–346.7) per 10,000 person-years, respectively. The incidence rate of MACE within 30/90/180/365 days was 4389.5 (3625.3–5314.8), 2760.1 (2387.8–3190.4), 2323.5 (2060.4–2620.2), and 1956.2 (1761.9–2172.0) per 10,000 person-years, respectively. The incidence of cardiovascular events was higher within 180 days after the initial prescription of ICI than after 180 days. During an observational period, 322 HF events were recorded. Among them, diuretics, renin-angiotensin system inhibitors, and beta-blockers were prescribed in 89, 36, and 37 patients within two months after the diagnosis of HF.

Table 1
Clinical characteristics.

	Overall (n = 2972)
Age, years	59 (53–65)
Men, n (%)	2163 (72.8)
Malignant Neoplasms	
Malignant Melanoma, n (%)	122 (4.1)
Lung Cancer, n (%)	1603 (53.9)
Renal Cell Cancer, n (%)	261 (8.8)
Hodgkin Lymphoma, n (%)	8 (0.3)
Head and Neck Cancer, n (%)	295 (9.9)
Stomach Cancer, n (%)	469 (15.8)
Esophagus Cancer, n (%)	184 (6.2)
Colorectal Cancer, n (%)	105 (3.5)
Urothelial Cancer, n (%)	173 (5.8)
Malignant Neoplasm without Specification of Site, n (%)	299 (10.1)
Merkel Cell Carcinoma, n (%)	32 (1.1)
Breast Cancer, n (%)	79 (2.7)
Liver Cancer, n (%)	88 (3.0)
Corpus Uteri Cancer, n (%)	27 (0.9)
Number of Cancers	
Single, n (%)	2284 (76.9)
Double, n (%)	560 (18.8)
Triple, n (%)	111 (3.7)
Unknown, n (%)	17 (0.6)
Medication	
Renin-angiotensin System Inhibitors, n (%)	485 (16.3)
Beta-blockers, n (%)	91 (3.1)
Glucose-lowering Medications, n (%)	298 (10.0)
Lipid-lowering Medications, n (%)	321 (10.8)
The type of Immune Checkpoint Inhibitor	
PD-1	2274 (76.5)
CTLA-4	4 (0.1)
PD-L1	584 (19.7)
Combination	110 (3.7)

Data are expressed as median (interquartile range) or number (percentage). PD-1 = programmed cell death-1. CTLA-4 = cytotoxic T lymphocyte-associated protein-4. PD-L1 = programmed cell death ligand 1.

Table 2
Number and incidence rate of cardiovascular events.

	Overall follow-up period (n = 2972)	Within 30 days of initial prescription	Within 90 days of initial prescription	Within 180 days of initial prescription	Within 365 days of initial prescription	After 180 days from initial prescription
Major adverse cardiac events						
Events	419 (14.1)	105	183	266	351	153
Incidence Rate	1583.9 (1439.2–1743.0)	4389.5 (3625.3–5314.8)	2760.1 (2387.8–3190.4)	2323.5 (2060.4–2620.2)	1956.2 (1761.9–2172.0)	1019.6 (870.2–1194.6)
Myocarditis						
Number of Events	1 (0.0)	0	0	1	1	0
Incidence Rate	3.4 (0.5–24.4)	0	0	8.3 (1.2–58.7)	5.2 (0.7–36.8)	0
Pericarditis						
Number of Events	41 (1.4)	8	11	23	29	18
Incidence Rate	142.3 (104.8–193.3)	328.5 (164.3–656.9)	159.9 (88.6–288.8)	190.8 (126.8–287.1)	151.1 (105.0–217.5)	107.4 (67.7–170.5)
Takotsubo cardiomyopathy						
Number of Events	3 (0.1)	0	1	2	3	1
Incidence Rate	10.3 (3.3–32.0)	0	14.5 (2.0–103.0)	16.5 (4.1–66.1)	15.5 (5.0–48.2)	5.9 (0.8–41.8)
Atrioventricular block						
Number of Events	5 (0.2)	1	1	3	3	2
Incidence Rate	17.2 (7.2–41.4)	41.0 (5.8–291.3)	14.5 (2.0–103.0)	24.8 (8.0–76.9)	15.6 (5.0–48.2)	11.8 (3.0–47.2)
Heart failure						
Number of Events	322 (10.8)	87	146	200	270	122
Incidence Rate	1191.2 (1068.0–1328.7)	3626.6 (2939.3–4474.7)	2185.4 (1858.2–2570.3)	1725.4 (1502.1–1981.9)	1480.2 (1313.8–1667.8)	790.2 (661.7–943.6)
Myocardial infarction						
Number of Events	16 (0.5)	2	7	10	14	6
Incidence Rate	55.2 (33.8–90.1)	82.1 (20.5–328.2)	101.7 (48.5–213.3)	82.8 (44.6–153.9)	72.7 (43.1–122.8)	35.5 (16.0–79.0)
Stroke						
Number of Events	80 (2.7)	15	30	50	64	30
Incidence Rate	278.5 (223.7–346.7)	616.7 (371.8–1022.9)	437.6 (305.9–625.8)	416.7 (315.8–549.8)	335.0 (262.2–428.0)	179.3 (125.4–256.5)

The incidence rate was per 10,000 person-years.

Table 3
Number of continuations of immune checkpoint inhibitors.

	Patients treated with ICI between two months prior to the onset of MACE	Patients who were re-prescribed ICI within two months after the onset of MACE
MACE		
Number	164	63 (38.4)
Myocarditis		
Number	1	0 (0.0)
Pericarditis		
Number	19	6 (31.6)
Takotsubo cardiomyopathy		
Number	3	0 (0.0)
Atrioventricular block		
Number	3	1 (33.3)
Heart failure		
Number	145	58 (40.0)
Myocardial infarction		
Number	4	0 (0.0)
Stroke		
Number	2	1 (50.0)

Data are expressed as number (percentage). Some events were recorded on the same day. Therefore, the sum of each component exceeds the number of MACEs (n = 164). ICI = immune-checkpoint inhibitor. MACE = major adverse cardiac event.

3.3. Prescription rate of ICI after the onset of MACE

Given the standard cancer treatment regimen using the ICIs in Japan, we extracted 164 patients treated with ICI between two months prior to MACE onset and MACE onset. Among them, 63 patients (38.4%) were re-prescribed ICI within two months after the onset of MACE. No patients were re-prescribed ICI within two months after the onset of myocarditis, Takotsubo cardiomyopathy or myocardial infarction, whereas 31.6% and 40.0% of patients were re-prescribed ICI within two months after the onset of pericarditis and HF, respectively (Table 3).

3.4. Characteristics of patients with and without MACE

Median age and sex were not different between patients with and without MACE. Lung cancer was more common in patients with MACE than those without MACE. The prescription status of ICI was similar between patients with and without MACE (Table 4). In the multivariable Cox model, the hazard ratio (95% confidence interval) for MACE was 0.86 (95% CI, 0.65–1.14) and 1.14 (95% CI, 0.64–2.04) for use of renin-angiotensin system inhibitors and use of beta-blockers (Table 5).

4. Discussion

Our analysis of a nationwide administrative claims dataset including approximately three thousand cancer patients treated with ICI showed that the incidence of HF was higher than expected and the most cardiovascular events occurred within 180 days after the initiation of ICI treatment. The re-prescription rate of ICI after the onset of cardiovascular events was relatively low. To the best of our knowledge, this is the first study demonstrating the incidence of CVD events among cancer patients requiring ICI treatment using a large-scale epidemiological database.

Preceding registry data showed the characteristics of patients treated with ICI [12,13]. Compared with these data, patients included in this study were relatively younger, which may be due to the nature of this database. The JMDC Claims Database primarily includes working-age population and does not include people aged ≥75 years. We need to recognize this point when we interpret the results of the present study. On the other hand, sex, the distribution of cancer sites (mainly lung cancers), and ICI regimen in this study were concordant with other data including cancer patients treated with ICI in Japan. In Europe and the United States, PD-1+CTLA4

Table 4
Clinical characteristics according to the major adverse cardiac events.

	Major adverse cardiac events (−) (n = 2553)	Major adverse cardiac events (+) (n = 419)	P value
Age, years	59 (53–65)	60 (52–65)	0.81
Men, n (%)	1853 (72.6)	310 (74.0)	0.55
Malignant neoplasms			
Malignant melanoma, n (%)	97 (3.8)	25 (6.0)	0.038
Lung cancer, n (%)	1335 (52.3)	268 (64.0)	<0.001
Renal cell cancer, n (%)	231 (9.0)	30 (7.2)	0.21
Hodgkin lymphoma, n (%)	6 (0.2)	2 (0.5)	0.37
Head and neck cancer, n (%)	263 (10.3)	32 (7.6)	0.091
Stomach cancer, n (%)	415 (16.3)	54 (12.9)	0.08
Esophagus cancer, n (%)	161 (6.3)	23 (5.5)	0.52
Colorectal cancer, n (%)	87 (3.4)	18 (4.3)	0.36
Urothelial cancer, n (%)	154 (6.0)	19 (4.5)	0.22
Malignant neoplasm without specification of site, n (%)	254 (9.9)	45 (10.7)	0.62
Merkel cell carcinoma, n (%)	26 (1.0)	6 (1.4)	0.45
Breast cancer, n (%)	71 (2.8)	8 (1.9)	0.3
Liver cancer, n (%)	80 (3.1)	8 (1.9)	0.17
Corpus uteri cancer, n (%)	25 (1.0)	2 (0.5)	0.32
Number of cancers			
Single, n (%)	1969 (77.1)	315 (75.2)	0.51
Double, n (%)	476 (18.6)	84 (20.0)	
Triple, n (%)	92 (3.6)	19 (4.5)	
Unknown, n (%)	16 (0.6)	1 (0.2)	
Medication			
Renin-angiotensin System Inhibitors, n (%)	425 (16.6)	60 (14.3)	0.23
Beta-blockers, n (%)	79 (3.1)	12 (2.9)	0.8
Glucose-lowering Medications, n (%)	254 (9.9)	44 (10.5)	0.73
Lipid-lowering Medications, n (%)	272 (10.7)	49 (11.7)	0.52
Type of immune checkpoint inhibitor			
PD-1	1942 (76.1)	332 (79.2)	0.39
CTLA-4	3 (0.1)	1 (0.2)	
PD-L1	514 (20.1)	70 (16.7)	
Combination	94 (3.7)	16 (3.8)	

Data are expressed as median (interquartile range) or number (percentage). PD-1 = programmed cell death-1. CTLA-4 = cytotoxic T lymphocyte-associated protein-4. PD-L1 = programmed cell death ligand 1.

Table 5
Multivariable Cox proportional hazard model result of the major adverse cardiac events.

	Hazard ratio (95% CI)	P value
Age	1.00 (0.99–1.01)	0.751
Male Sex	1.03 (0.82–1.28)	0.820
Lung cancer	1.19 (0.97–1.46)	0.104
Use of renin-angiotensin system inhibitors	0.86 (0.65–1.14)	0.303
Use of beta-blockers	1.14 (0.64–2.04)	0.654
Type of immune checkpoint inhibitor		
PD-1	1 (Reference)	
CTLA-4	1.64 (0.23–11.76)	0.621
PD-L1	0.84 (0.64–1.09)	0.187
Combination	1.31 (0.78–2.18)	0.295

95% CI = 95% confidence interval. PD-1 = programmed cell death-1. CTLA-4 = cytotoxic T lymphocyte-associated protein-4. PD-L1 = programmed cell death ligand 1.

combination therapy is widely used for malignant melanoma. On the other hand, the frequency of combination therapy is low in Japan because malignant melanoma is less common in Japan and the indication for combination therapy of ICIs is limited to certain types of colorectal cancer and renal cell carcinoma. In this study, the combination therapy rate was only 3.7%. Taking these points into consideration, although lack of data for elderly patients should be recognized as a study limitation, we believe that our dataset could be considered a snapshot of cancer patients treated using ICI.

Acute myocarditis is the most serious complication of cardiovascular events occurring with the ICI use. The incidence of myocarditis after ICI use varies with each investigation [8,13–17]. In this study, myocarditis was recorded in only one patient, with an incidence of 0.03%, which is lower than previously reported. However, Takotsubo cardiomyopathy was documented in three patients, its incidence is consistent with earlier investigations [15,18–20]. The incidence of MI was also close to the reported value in the previous meta-analysis [21]. On the other hand, the incidence of HF and stroke was higher than expected. This may be due to the fact that the JMDC Claims Database includes diagnoses which were made in not only inpatient settings but also outpatient settings. Unfortunately, the JMDC Claims Database is unable to distinguish between diagnoses made in the inpatient or outpatient settings. Further, more than 40% of patients developing HF were newly prescribed diuretics and/or cardioprotective medication, suggesting that a substantial proportion of patients diagnosed with HF required any medical treatments. These results indicate that HF, even in outpatients, is more common than expected and clinically problematic in patients requiring ICI treatment. The results reaffirm the importance of cardio-oncology.

The continuation rate of ICI was low in patients developing MACE. Given the nature of our dataset, we could not conclude that the occurrence of MACE led to the discontinuation of the treatment using ICI. However, it is highly plausible that treatment with ICI was discontinued (or interrupted) due to the occurrence of MACE. Considering the clinical importance of MACE, it is required to identify the predictors of MACE. As previously reported [8,22], age and gender were not associated. On the other hand, although ICI combination treatment was reported to be associated with MACE (particularly myocarditis) in preceding studies [4,15], the association of ICI combination treatment with MACE was not significant, which may be due to the low rate of ICI combination treatment in this study. Further, some evidence exists that cardiovascular drugs might prevent cardiac dysfunction after treatment of malignant neoplasms [23–25]; however, we found no significant association of the renin-angiotensin system inhibitors use and beta-blockers use with the risk of MACE. We need further investigations to uncover the predictors of MACE after the treatment using ICI and establish the preventive measures for cardiovascular events among cancer patients requiring ICI treatment.

There are several strengths in our study. Approximately 3000 patients treated with ICI participated in this extensive population-based investigation. The JMDC Claims Database also has a high retention rate for research participants. Since this database contains the administrative claims records and Japan has a universal health insurance system for the entire Japanese population, all CVD events can theoretically be monitored even if patients enrolled in this study visited multiple medical facilities. The patients treated with ICI are patients with advanced stage cancer and frequently have a number of comorbidities. Loss to follow-up is more likely to occur in such patients because patients are likely to visit many health care providers (different hospitals). In this study, the use of the JMDC Claims Database may have allowed us to follow study participants over a relatively long period of time.

We acknowledge several potential limitations in the present study. The accuracy (particularly, specificity) of insurance claims records in Japan is reported to be high [26,27]. However, we acknowledge that there remains uncertainty about the accuracy of the diagnoses and prescriptions using administrative claims data. Our results should be validated using other independent datasets. Detailed information on cancer (e.g., cancer stage) and prescription history before insurance coverage was unavailable. The incidence of CVD events may be underestimated because death could be considered as a competing risk. Lastly, it cannot be claimed that all of the cardiovascular events recorded in this study (including HF) were adverse events of ICI. However, given that the onset of cardiovascular events is skewed toward those within the first few months of initiation of treatment using ICI, we should consider that treatment with ICI would have some influence on many of these cardiovascular events.

In conclusion, we conducted a comprehensive analysis of the incidence of CVD events after the initiation of ICI treatment in cancer patients using a large-scale administrative claims database. Among CVD events, the incidence of HF was higher than expected. The rate of ICI re-prescriptions after the documentation of CVD events was low, indicating the clinical importance of CVD events in cancer patients requiring the ICI treatment.

Data availability

The JMDC Claims Database is available for purchase from JMDC Inc. (https://www.jmdc.co.jp/en/).

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Author contribution statement

Yuta Suzuki; Hidehiro Kaneko; Yuichi Tamura; Akira Okada; Katsuhito Fujiu; Norifumi Takeda; Hiroyuki Morita; Koichi Node; Issei Komuro: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.

Nobuaki Michihata; Taisuke Jo; Hideo Yasunaga: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tool or data; Wrote the paper.

Declaration of competing interest

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

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