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Abdominal aortic calcification in patients newly diagnosed with essential thrombocythemia

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Background
Although atherosclerosis is likely to be involved in the development of arterial thrombotic events in patients with essential thrombocythemia (ET), abdominal aortic calcification (AAC) has rarely been investigated. We evaluated the prevalence and clinical relevance of AAC at the time of ET diagnosis.

Methods
This retrospective study included patients newly diagnosed with ET who underwent abdominal computed tomography (CT) at the time of diagnosis between January 2002 and December 2021 at Chungnam National University Hospital, Daejeon, Korea. CT images were reviewed and an aortic calcification score was assigned.

Results
Of the 94 patients (median age, 62 yr; range, 18–90 yr), AAC was detected in 62 (66.0%). AAC was most commonly mild (33.0%), followed by moderate (22.7%) and severe (5.3%). Old age [odds ratio (OR), 34.37; 95% confidence interval (CI), 12.32–95.91; $P<0.001$] was an independent risk factor for AAC. The patients with AAC had a higher WBC count (11.8±4.7 vs. 9.7±2.9×10^9/L, $P=0.017$), higher neutrophil-to-lymphocyte ratio (4.3±2.7 vs. 3.1±1.5, $P=0.039$), and higher *JAK2*V617F positivity (81.5% vs. 58.8%, $P=0.020$) compared to those without AAC. AAC was an independent risk factor for arterial thrombotic vascular events that occurred before or at diagnosis of ET (OR, 4.12; 95% CI, 1.11–15.85; $P=0.034$).

Conclusion
AAC is common in patients with ET and is associated with arterial thrombotic events.

Key Words Essential thrombocythemia, Atherosclerosis, Abdominal aortic calcification, Arterial thrombosis

INTRODUCTION

Philadelphia chromosome-negative myeloproliferative neoplasms (Ph$^-$ MPNs) are clonal hematological disorders that include essential thrombocythemia (ET), polycythemia vera, and primary myelofibrosis. These disorders are characterized by an increased blood cell count, frequent thrombotic vascular events [1], and myelofibrotic or leukemic transformation [2]. Thrombotic vascular events in Ph$^-$ MPN patients often lead to significant morbidity and mortality. Arterial thrombotic events are significantly more common than venous events, with acute coronary syndrome and cerebral infarction being the most common vascular events [1, 3-6].

Arterial thrombosis is commonly associated with atherosclerosis, which is a chronic inflammatory vascular disorder [7]. Accumulating evidence indicates that inflammation is involved in the pathophysiology of Ph$^-$ MPNs and several symptoms and signs in Ph$^-$ MPN patients result from inflammation [8-10]. In *JAK2*V617F mice, inflammation promotes the development and progression of atherosclerosis [11]. Additionally, clonal hematopoiesis due to somatic mutations is a relatively common and independent risk factor

for atherosclerotic cardiovascular disease and other cardiovascular conditions [7, 12, 13]. In particular, hematopoietic cell clones harboring *JAK2*V617F, the most frequent driver mutation in Ph$^-$ MPNs, are causally associated with the pathogenesis of cardiovascular diseases [7, 12]. Taken together, atherosclerosis is likely to be involved in arterial thrombotic events in Ph$^-$ MPN patients; however, limited studies exist on the prevalence and severity of atherosclerosis in these patients.

Several tools are used to identify and measure the degree of atherosclerosis and, thus, the vascular risk, including measuring the carotid artery wall thickness [14], arterial pulse wave velocity [15], coronary artery calcium deposition [16], and thoracic or abdominal aortic calcification (AAC) [17, 18]. Arterial calcification is the end stage of stabilized atherosclerotic plaques, and AAC is considered a predictor of vascular morbidity and mortality [19, 20]. However, AAC has seldom been evaluated in Ph$^-$ MPN patients. In the present study, we retrospectively evaluated the prevalence and clinical relevance of AAC in patients with ET by using abdominal computed tomography (CT) performed at the time of diagnosis.

MATERIALS AND METHODS

Patients

We reviewed the medical records of patients diagnosed with ET who underwent abdominal CT at the time of diagnosis (between January 2002 and December 2021) at Chungnam National University Hospital, Daejeon, Korea. Before 2016, abdominal CT was performed to identify patients with splenomegaly, verify the diagnosis, and investigate relevant symptoms or signs. After 2016, abdominal CT has been routinely performed for the initial evaluation of patients at the time of diagnosis. For patients diagnosed with ET before 2017, the diagnosis was revised based on the 2016 World Health Organization diagnostic criteria [21]. Hydroxyurea or anagrelide was prescribed for cytoreduction, based on standard recommendations, drug availability, and patient compliance. In addition, except for low- or very low-risk patients, low-dose aspirin (100 mg daily) was administered to prevent thrombosis.

Driver gene mutation analyses

The presence of *JAK2*V617F was identified using polymerase chain reaction (PCR) and Sanger sequencing before 2010 and using allele-specific real-time quantitative PCR after 2010. A *CALR* mutation in exon 9 was detected using fragment analysis and Sanger sequencing. The presence of *MPL*W515K/L mutation was assessed by PCR and Sanger sequencing.

Computed tomography

Computed tomography (CT) was performed using various scanners and techniques, although most CT images were obtained using the following multidetector CT scanners: SOMATOM Sensation 16, SOMATOM Sensation 64, SOMATOM Definition Edge, and SOMATOM Definition Flash (Siemens Medical Solutions, Forchheim, Germany). The scanning parameters were as follows: section thickness, 3.0–5.0 mm; field of view, 304–360 mm; tube current-time product, 144–486 mAs; and peak voltage, 100–120 kVp. After acquisition of the un-enhanced scans, contrast-enhanced scans were obtained. In total, 1.2–1.5 mL of non-ionic contrast material [iopromide (370 mg iodine/mL), Ultravist 370; Bayer Healthcare, Berlin, Germany] per kg of body weight was injected into the patient's antecubital vein at a rate of 3–4 mL/s, using a power injector. A bolus tracking technique was used to optimize the timing of the arterial phase scan. Late portal phase images were obtained 70–80 s after contrast injection. A 20 mL flush of normal saline solution was administered immediately after contrast injection. Most of the axial CT images were reconstructed with a section thickness of 3 mm.

Measuring the aortic calcification score (ACS)

Calcium in the abdominal aortic wall was quantified using dedicated post-processing software (Philips Intellispace Portal 10.0, Philips Healthcare, Amsterdam, the Netherlands) and the Agatston method [22]. ACS was calculated by multiplying the lesion area by an attenuation factor derived from the maximal Hounsfield units within the area. This tool uses a threshold of 130 HU and region-growing algorithms. A radiologist who was blinded to the clinical data and outcomes drew the regions of interest around the vessel of interest on the supine axial images of the abdominal aorta (from the level of the diaphragmatic crus to the aortic bifurcation), while excluding the main branches of the vessels. The colored areas of calcification were reviewed on three-dimensional axial, sagittal, and coronal views, and the regions of interest were edited using a dedicated post-processing software until satisfactory results were obtained. AAC was arbitrarily classified as none (ACS <10), mild (ACS 10–999), moderate (ACS 1,000–10,000), or severe (ACS $>10,000$).

Definition of splenomegaly

Splenomegaly was defined as follows: "palpable splenomegaly" indicated that the spleen was palpable below the left costal margin and "volumetric splenomegaly" indicated that the spleen volume was larger than the mean volume plus three standard deviations of the reference volumes, based on the age and body surface area of the patient [23].

Definitions of thrombotic vascular events

Thrombotic vascular events included cerebrovascular (ischemic stroke, transient ischemic attack, and venous sinus thrombosis), coronary (any ischemic heart disease diagnosed using coronary angiography, including acute coronary syndrome), splanchnic, and peripheral thromboembolisms. All events that occurred before, at, and after diagnosis were included in the analysis.

Statistical analysis

Descriptive data are presented as means±standard deviation, median (range), or percentage, and were analyzed using Student's t-test, chi-square test, or Fisher's exact test, as appropriate. Correlations between the AAC and other parameters were assessed using Pearson's correlation analysis. The risk factors for AAC at the time of ET diagnosis and arterial thrombotic vascular events that occurred before or at the time of ET diagnosis were analyzed using a binary logistic regression model. Statistical analyses were performed using SPSS (version 24.0, IBM, Armonk, NY, USA), and $P<0.05$ was considered to indicate statistical significance.

Table 1. Patient characteristics (N=94).

Age, yr, median (range)	62 (18–90)
Male	45 (47.9)
Time of diagnosis	
2002–2015	27 (28.7)
2016–2021	67 (71.3)
Palpable splenomegaly	0 (0.0)
Volumetric splenomegaly	47 (50.0)
Laboratory findings	
WBC, $\times10^9$/L	11.0±4.2
Neutrophil/lymphocyte	3.9±2.4
Monocyte, $\times10^9$/L	0.6±0.5
Hemoglobin, g/dL	13.6±2.2
Platelet, $\times10^9$/L	948.2±387.7
LDH, ×ULN	1.2±0.4
Driver gene mutation	
*JAK2*V617F	64 (72.8)
CALR	9 (9.6)
MPL	3 (3.2)
*JAK2*V617F VAF, %	24.8±12.8
IPSET	
Low	30 (31.9)
Intermediate	27 (28.7)
High	37 (39.4)
Comorbidity	
Hypertension	32 (34.0)
Diabetes mellitus	12 (13.8)
Chronic kidney disease	11 (11.7)
Dyslipidemia	19 (20.2)
Smoking	21 (22.3)
Treatments	
Cytoreductive treatment	65 (67.4)
Aspirin	86 (91.5)
Initial thrombotic events	
Time of occurrence	
Before or at diagnosis	21 (22.3)
After diagnosis	1 (1.1)
Overall	22 (23.4)
Vessels involved	
Arterial	21 (22.3)
Venous	1 (1.1)
Follow-up, yr, median (range)	2.9 (0.12–0.2)

Values are presented as number (%) or mean±standard deviation.
Abbreviations: *CALR*, calreticulin; IPSET, International Prognostic Score in Essential Thrombocythemia; LDH, lactate dehydrogenase; ULN, upper limit of normal; VAF, variant allele frequency.

Ethics

This study was approved by the Institutional Review Board of the Chungnam National University Hospital (IRB No. CNUH 2022-01-069). The need for informed patient consent was waived due to the retrospective nature of the study.

RESULTS

Patient characteristics

During the study period, 136 patients were diagnosed with ET. Of these patients, 94 (69.1%) with a median age of 62 years (range, 18–90 yr) were enrolled in the study. They were followed up for a median of 2.9 years (range, 0.1–20.2 yr). Patients were evenly distributed across the International Prognostic Score in ET (IPSET) risk groups [24]. *JAK2*V617F was detected in 64 (72.8%) patients. Cytoreductive therapy was prescribed to 65 (67.4%) patients. Most of the patients were prescribed low-dose aspirin. Thrombotic vascular events occurred in 22 (23.4%) patients. Most thrombotic vascular events (95.5%) occurred soon before or at the time of ET diagnosis. Arterial events (95.5%) were more common than venous events (4.5%) (Table 1).

Prevalence and severity of AAC at the time of ET diagnosis

Of the 94 study patients, AAC was detected in 62 (66.0%). AAC was most commonly mild (33.0%), followed by moderate (22.7%) and severe (5.3%). The ACS in these patients was 1,521±2,985 (Table 2).

Risk factors for AAC at the time of ET diagnosis

Logistic regression analysis was performed to identify risk factors for AAC detection at the time of diagnosis. Univariate analysis showed that old age (>60 yr), leukocytosis (>11.0×10^9/L), monocytosis (>1.0×10^9/L), positive *JAK2*V617F, hypertension, diabetes mellitus, and dyslipidemia were risk factors for AAC detection. Multivariate analysis showed that old age [odds ratio (OR), 34.37; 95% confidence interval (CI), 12.32–95.91; $P<0.001$] was an independent risk factor

Table 2. Prevalence and severity of abdominal aortic calcification (N=94).

Severity of calcification[a)]	N (%)	Aortic calcification score (ACS)
No	32 (24.0)	4±5
Mild	31 (33.0)	413±368
Moderate	26 (27.7)	2,814±1,783
Severe	5 (5.3)	12,365±5,238
Total	94 (100)	1,521±2,985

[a)]Abdominal aortic calcification was arbitrarily classified as no calcification (ACS <10), mild calcification (ACS of 10–999), moderate calcification (ACS of 1,000–10,000), or severe calcification (ACS > 10,000).

of AAC (Table 3). The ACS was positively correlated with age (r=0.451, P<0.001), white blood cell (WBC) count (r=0.320, P=0.002), neutrophil-to-lymphocyte ratio (r=0.235, P=0.024), and monocyte count (r=0.391, P<0.001) (Fig. 1), but not with the spleen volume (r=-0.131, P=0.315), platelet count (r=0.156, P=0.137), LDH level (r=-0.005, P=0.966), or *JAK2*V617F variant allele frequency (VAF) (r=0.166, P=0.129).

Table 3. Risk factors for developing abdominal aortic calcification at diagnosis of essential thrombocythemia (N=94).

	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P*	OR	95% CI	*P*
Age >60 yr	28.23	12.31–64.88	<0.001	34.37	12.32–95.91	<0.001
Male	2.00	0.85–4.72	0.111	-	-	-
Volumetric splenomegaly	1.07	0.59–2.03	0.833	-	-	-
WBC >11.0×10^9/L	2.66	1.12–6.96	0.028	3.92	0.93–16.50	0.062
Monocyte >1.0×10^9/L	6.94	1.59–20.33	0.010	4.38	0.25–77.29	0.313
Neutrophil/lymphocyte >4.0	2.28	0.88–5.90	0.089	-	-	-
Platelet >1,000×10^9/L	1.29	0.61–2.72	0.509	-	-	-
LDH >1.5×ULN	3.32	0.88–12.51	0.076	-	-	-
Positive *JAK2*V617F	3.41	1.17–8.11	0.023	3.16	0.66–15.23	0.151
Positive *CALR* mutation	0.44	0.11–1.75	0.242	-	-	-
Hypertension	5.06	1.73–14.85	0.003	1.05	0.17–6.61	0.955
Diabetes mellitus	3.97	1.07–14.79	0.040	4.74	0.41–54.23	0.211
Chronic kidney disease	6.94	0.85–56.76	0.071	-	-	-
Dyslipidemia	3.97	1.09–14.79	0.040	5.05	0.85–30.21	0.076
Smoking	1.65	0.57–4.74	0.354	-	-	-

Abbreviations: *CALR*, calreticulin; CI, confidence interval; LDH, lactate dehydrogenase; OR, odds ratio; ULN, upper limit of normal.

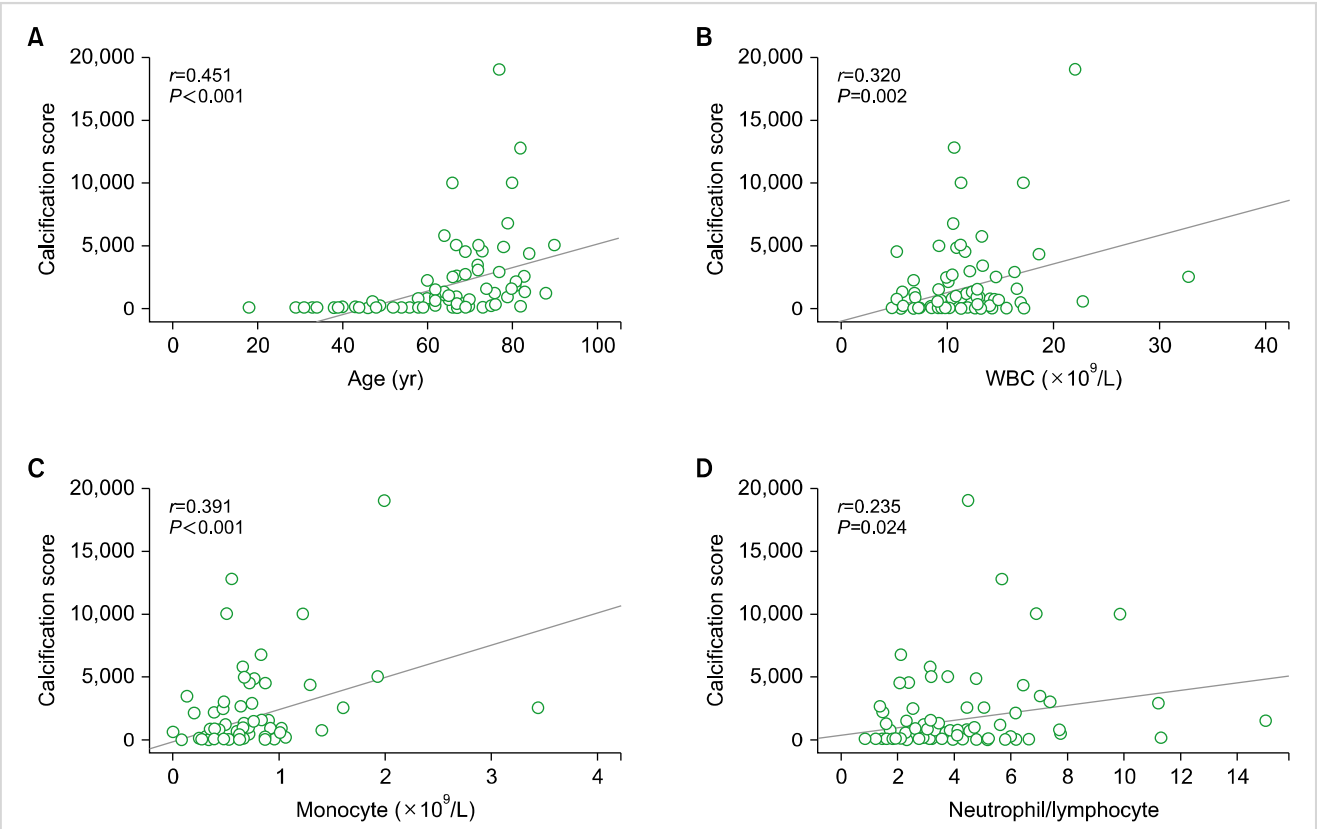

Fig. 1. Correlations between aortic calcification score and various parameters: **(A)** age, **(B)** white blood cell count, **(C)** monocyte count, and **(D)** neutrophil-to-lymphocyte ratio.

Comparison of ET patients according to AAC status

ET patients with AAC were older than those without AAC (68.1±10.5 vs. 49.4±12.3 yr, respectively; $P<0.001$). Sex and rate of volumetric splenomegaly did not differ according to the presence or absence of AAC in patients with ET. The patients with AAC exhibited a higher WBC count (11.8±4.7 vs. 9.7±2.9×10^9/L, respectively; $P=0.017$), higher neutrophil-to-lymphocyte ratio (4.3±2.7 vs. 3.1±1.5, respectively; $P=0.039$), higher monocyte count (0.7±0.5 vs. 0.5±0.2×10^9/L, respectively; $P=0.003$), higher LDH normalized ratio (1.3±0.4 vs. 1.1±0.4, respectively; $P=0.043$), and higher *JAK2*V617F positivity (81.5% vs. 58.8%, respectively; $P=0.020$) compared to those without AAC. A greater number of ET patients with AAC belonged to the higher-risk group than those without AAC according to IPSET (high risk, 59.9% vs. 11.4%, respectively; $P<0.001$) and revised IPSET thrombosis (high risk, 71.2% vs. 14.3%, respectively; $P<0.001$) [25]. Hypertension (45.8% vs. 14.3%, $P=0.002$), chronic kidney disease (16.9% vs. 5.7%, $P=0.030$), and dyslipidemia (27.1% vs. 8.6%, $P=0.001$), but not diabetes mellitus or smoking, were more common in patients with ET with AAC than in those without AAC. Arterial thrombotic events (30.5% vs. 8.6%, $P=0.014$) and thrombotic vascular events (32.2% vs. 8.6%, $P=0.009$) were more common in patients with ET with AAC than in those without AAC (Table 4).

Risk factors for arterial thrombotic vascular events

Logistic regression analysis was performed to identify risk factors for arterial thrombotic events that occurred before or at the time of ET diagnosis. Univariate analysis showed that old age (>60 yr), high neutrophil-to-lymphocyte ratio (>4.0), positive *JAK2*V617F, chronic kidney disease, and AAC were risk factors for arterial thrombotic vascular events. The multivariate analysis showed that AAC was an in-

Table 4. Clinical features of essential thrombocythemia patients according to abdominal aortic calcification.

	Without AAC (N=35)	With AAC (N=59)	*P*
Age, yr	49.4±12.3	68.1±10.5	<0.001
Male	12 (37.1)	32 (54.2)	0.109
Volumetric splenomegaly	18 (51.4)	29 (49.2)	0.831
Laboratory findings			
WBC, ×10^9/L	9.7±2.9	11.8±4.7	0.017
Neutrophil/lymphocyte	3.2±1.5	4.3±2.7	0.039
Monocyte, ×10^9/L	0.5±0.2	0.7±0.5	0.003
Hemoglobin, g/dL	14.0±1.6	13.2±2.5	0.111
Platelet, ×10^9/L	881.3±338.2	989.3±412.6	0.196
LDH, ×ULN	1.1±0.4	1.3±0.4	0.043
Driver gene mutation			
*JAK2*V617F	20 (58.8)	44 (81.5)	0.020
CALR	5 (14.3)	4 (6.8)	0.232
*JAK2*V617F VAF, %	21.8±11.0	26.1±13.5	0.218
IPSET			<0.001
Low	26 (74.3)	3 (5.1)	
Intermediate	5 (14.3)	23 (39.0)	
High	4 (11.4)	33 (55.9)	
R-IPSET-T			<0.001
Very low	11 (31.4)	1 (1.7)	
Low	17 (48.6)	6 (10.2)	
Intermediate	1 (2.9)	10 (16.9)	
High	5 (14.3)	42 (71.2)	
Comorbidity			
Hypertension	5 (14.3)	27 (45.8)	0.002
Diabetes mellitus	2 (5.7)	11 (18.6)	0.079
Chronic kidney disease	1 (2.9)	10 (16.9)	0.030
Dyslipidemia	3 (8.6)	16 (27.1)	0.001
Smoking	6 (17.1)	15 (25.4)	0.351
Thrombotic event			
Arterial	3 (8.6)	18 (30.5)	0.014
Overall	3 (8.6)	19 (32.2)	0.009
Hemorrhagic event	1 (2.9)	7 (11.9)	0.130
Follow-up, yr	6.3±5.8	3.2±3.6	0.002

Data are presented as number (%) or mean±standard deviation.
Abbreviations: AAC, abdominal aortic calcification; *CALR*, calreticulin; IPSET, International Prognostic Score in Essential Thrombocythemia; LDH, lactate dehydrogenase; R-IPSET-T, revised IPSET-thrombosis; ULN, upper limit of normal; VAF, variant allele frequency.

Table 5. Risk factors for thrombotic vascular events occurring before or at diagnosis of essential thrombocythemia (N=94).

	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P*	OR	95% CI	*P*
Age >60 yr	3.59	1.20–10.79	0.023	1.52	0.35–6.72	0.578
Male	1.42	0.54–3.70	0.475	-	-	-
Volumetric splenomegaly	0.37	0.14–1.03	0.056	-	-	-
WBC >11.0×10^9/L	0.67	0.64–4.36	0.298	-	-	-
Monocyte >1.0×10^9/L	2.06	0.54–7.84	0.287	-	-	-
Neutrophil/lymphocyte >4.0	3.22	1.20–8.68	0.021	1.84	0.57–5.69	0.322
Platelet >1,000×10^9/L	2.33	0.86–6.25	0.095	-	-	-
LDH >1.5×ULN	1.01	0.29–3.48	0.989	-	-	-
Positive *JAK2*V617F	2.87	1.05–8.63	0.048	2.33	0.75–7.18	0.142
Hypertension	1.57	0.59–4.22	0.368	-	-	-
Diabetes mellitus	2.35	0.68–8.12	0.176	-	-	-
Chronic kidney disease	5.03	1.36–18.55	0.015	3.66	0.95–14.06	0.059
Dyslipidemia	0.84	0.25–2.87	0.787	-	-	-
Smoking	1.93	0.66–5.64	0.227	-	-	-
AAC	5.07	1.38–18.65	0.015	4.12	1.11–15.85	0.034

Abbreviations: AAC, abdominal aortic calcification; CI, confidence interval; LDH, lactate dehydrogenase; OR, odds ratio; ULN, upper limit of normal.

dependent risk factor for arterial thrombotic vascular events (OR, 4.12; 95% CI, 1.11–15.85; *P*=0.034) (Table 5).

DISCUSSION

This study investigated the prevalence and severity of AAC and its clinical implications in 94 patients, newly diagnosed with ET. To the best of our knowledge, this is the first study to evaluate AAC in patients with ET. The prevalence of AAC in the study patients was 66.0%, which was considerably higher than that (28.8%) reported in the US population [26] or that (35.1%) reported in a study of Korean patients with chronic kidney disease [18], even if the age difference between the study groups was considered.

Previous studies on various populations revealed that old age, male sex, hypertension, diabetes mellitus, smoking, chronic kidney disease, and dyslipidemia were risk factors for AAC [19, 20]. In the patients included in the present study, old age was the only independent risk factors for AAC. Leukocytosis and *JAK2*V617F were identified as risk factors for AAC in the univariate analysis, however they were not statistically significant in the multivariate analysis. ACS was well correlated not only with age, but also with WBC count and neutrophil-to-lymphocyte ratio. Leukocytosis and *JAK2*V617F positivity were significantly more common in patients with AAC than in those without AAC, suggesting that they are involved in the development of AAC, at least in a subpopulation of patients with ET. Considering the limited number of patients in this study, further studies with larger sample sizes are required to confirm these findings.

The patients with AAC differ from those without AAC in several ways. Patients with AAC were significantly older than those without AAC. Old age is a risk factor of both arteriosclerosis and atherosclerosis [27-31]. In general, the clinical parameters of AAC patients suggest the presence of an advanced disease stage or poor prognosis. The patients with AAC had higher WBC counts, neutrophil-to-lymphocyte ratios, and monocyte counts than those without AAC. Furthermore, patients with AAC had a higher rate of arterial thrombotic events that occurred soon before or at the time of ET diagnosis than patients without AAC. The majority of vascular events were arterial events that occurred soon before or at the time of ET diagnosis in the present study population Therefore, we focused on the clinical impact of AAC on these vascular events. AAC was an independent risk factor of arterial thrombotic events that occur before or at the time of ET diagnosis. Old age was a risk factor for arterial thrombosis in the univariate analysis but not in the multivariate analysis, suggesting that old age is associated with atherosclerosis. Collectively, our results suggest that arterial thrombotic vascular events occur in the background of atherosclerosis in a major subpopulation of patients with ET. Accordingly, the development of atherosclerosis explains the higher prevalence of arterial vascular events than of venous events, in these patients. In the present study, thrombotic vascular events occurred infrequently after the diagnosis of ET. Therefore, the relationship between the presence of AAC at the time of ET diagnosis and vascular events during the clinical course could not be evaluated. In addition, whether additional measures are required to prevent thrombosis in patients with AAC at the time of diagnosis remains to be determined; thus, further studies are warranted.

Abdominal CT is not routinely performed during the initial evaluation of ET patients [32]. The clinical relevance of volumetric splenomegaly and splenic infarction detected using

abdominal CT performed at the time of diagnosis of Ph- MPN has been previously evaluated [23, 33, 34]. Furthermore, in a small proportion of patients, abdominal CT has been used to detected asymptomatic malignancies at the time of diagnosis of Ph- MPN. In the present study, we report the clinical relevance of AAC detected using abdominal CT in patients with ET. Based on these observations, we propose that abdominal CT should be performed during the initial evaluation of patients with ET.

The present study has certain limitations. First, this study enrolled a subpopulation rather than the entire population of patients, with ET diagnosed during the study period.Therefore, the results may not be applicable to all patients with ET. Second, the study patients were not compared with controls matched to the patients, according to their age and relevant parameters. Third, this study did not thoroughly investigate whether AAC is a predictor of vascular events occurring after ET diagnosis. Despite these limitations, our results show that AAC is common in patients with ET and associated with arterial thrombotic events.

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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