Disease activity as a risk factor for venous thromboembolism in rheumatoid arthritis analysed using time-averaged DAS28CRP: a nested case-control study

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Author contributions M.Y., Y.F., and T.A. conceived the study. M.Y. and Y.F. were responsible for data collection, acquisition, and analysis. I.Y and Y.M.I. contributed to the design and statistical methods. M.Y., Y.F. and T.A were involved in the interpretation of the material. M.Y. wrote the first draft of the paper. M.Y. and Y.F. were responsible for critical revision of the manuscript. M.S., M.K., M.K., O.M., and T.A. helped supervise the project. All authors contributed to the discussion and approved the final version of the manuscript. All authors and co-authors take full responsibility for the integrity and accuracy of the work in all aspects.

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Conflict of interest

T. Atsumi reports grants from Astellas, Takeda Pharmaceutical, Mitsubishi Tanabe, Chugai Pharmaceutical, Daiichi Sankyo, Otsuka Pharmaceutical, Pfizer, and Alexion, and personal fees from Mitsubishi Tanabe, Chugai Pharmaceutical, Astellas, Takeda Pharmaceutical, Pfizer, AbbVie, Eisai, Daiichi Sankyo, Bristol-Myers Squibb, UCB Japan, Eli Lilly Japan, AstraZeneca, MEDICAL & BIOLOGICAL LABORATORIES, ONO PHARMACEUTICAL, Novartis, and Nippon Boehringer Ingelheim, outside the submitted work. M. Kato has received research grants from AbbVie, Actelion, and GlaxoSmithKline and speaking fees from Eli Lilly. M. Kono has received research grants from GlaxoSmithKline plc, Mitsubishi Tanabe, Astellas, Sanofi, Taisho Pharmaceutical, and Taisho Pharmaceutical, outside the submitted work. The other authors state that they have no conflict of interest.

ABSTRACT

[Objective] To clarify the clinical features and risk factors of venous thromboembolism (VTE) in patients with rheumatoid arthritis (RA).

[Methods] We retrospectively reviewed the prevalence of VTE in RA patients who visited Hokkaido University Hospital from 2010 to 2019 and had more than 2 years follow-up. To explore the risk to develop VTE, we selected 260 RA patients without VTE (non-VTE)

via density sampling and identified the risk factors for VTE by multivariate logistic regression analysis.

[Results] Univariate conditional logistic regression analysis showed older age ($p < 0.0001$, Odds Ratio [OR] 1.08, 95% Confidence Interval [CI] 1.04-1.14), increase of the body mass index (BMI) ($p = 0.001$, OR 1.17, 95% CI 1.06-1.31), higher prevalence of RA-associated lung disease ($p = 0.002$, OR 2.10, 95% CI 1.33-3.30) and more frequent glucocorticoid usage ($p = 0.001$, OR 2.09, 95% CI 1.34-3.51) in RA patients was associated with the development of VTE significantly. Furthermore, patients with higher time-averaged disease activity score 28 (DAS28) CRP were at elevated risk ($p < 0.0001$, OR 3.25, 95% CI 1.94-6.12). In conditional multivariate logistic regression analysis, time averaged DAS28CRP was significantly associated with the development of VTE ($p = 0.0001$, adjusted OR 3.40, 95% CI 1.77-7.85).

[Conclusion] Disease activity was identified as a major risk factor of VTE in patients with RA, suggesting that sustained clinical remission could be beneficial for decrease the risk of VTE.

Keywords: Rheumatoid arthritis, venous thromboembolism, disease activity, time-averaged DAS28CRP

Disease activity in patients with rheumatoid arthritis associate between development of venous thromboembolism and analysed using time-averaged DAS28CRP: a nested case-control study

Introduction

Venous thromboembolism (VTE), which manifests as deep vein thrombosis or pulmonary embolism, is a common and potentially fatal condition. Early diagnosis and treatment are required to prevent substantial morbidity and mortality. The risk factors for VTE include genetic factors and racial differences, as well as increasing age, prolonged immobility, malignancy, surgical operation, multiple traumas, and prior history of VTE [1, 2]. In addition, systemic chronic inflammation is associated with a high risk of developing VTE, since it causes platelet aggregation, vascular endothelial damage, and coagulation abnormalities [3-7]. Systemic chronic inflammation affects the Virchow's triad [8], which proposes that VTE is triggered by vascular endothelial damage, stagnated blood flow, and hypercoagulability.

Rheumatoid arthritis is a chronic inflammatory disease, which may lead to irreversible disability due to cartilage and bone damage in multiple joints [9]. Improvement of prognosis and quality of life in RA patients depends on controlling joint destruction, managing comorbidities and extraarticular symptoms including thrombosis [10]. Indeed, RA is one of the most established risk factors for VTE development [11-17]. Elevated serum levels of C-reactive protein (CRP), interleukin (IL)-6, IL-8, and tumour necrosis factor alpha (TNFa), which occur in patients with sustained inflammation, are associated with susceptibility of thrombosis in patients with RA [18-21]. Recently, Molander V, et

al [22] reported an association between RA disease activity and VTE in a large Swedish cohort. However, changes in disease activity over time were not discussed in the article. DAS28 assessed at only one point may not be sufficient to evaluate RA disease activity in a given patient, since comorbidities such as malignancy or infection can modify DAS28 scores, and more importantly, DAS28 would fluctuate during the course of the disease.

The methods to represent overall disease activity in a RA patient include "time-integrated values of DAS28" defined as area under the curve [23], or "time-averaged DAS28", which is a mathematical model using time-integrated values to assess inflammation due to RA over time [24]. Values obtained by these methods could be more appropriate to represent overall disease activity, which reflects the accumulated history of inflammation in clinical observational studies of RA.

The aim of this study was to assess the clinical features of Japanese RA patients with VTE and investigate the association between RA disease activity evaluated by "time-averaged DAS28" and the development of VTE.

Methods

Patients and Methods

We conducted a single-centre, retrospective study at Hokkaido University Hospital in accordance with the ethical principles of Declaration of Helsinki and the Good Clinical Practice guidelines approved by Hokkaido University Hospital Ethics Committee (approval number: 020-0072).

We extracted the data of adult RA patients (aged ≥ 18 years) who visited our hospital from January 2010 to June 2019 with at least 2 years of follow-up. All patients fulfilled the 2010 American College of Rheumatology (ACR)/ European League Against Rheumatism (EULAR) classification criteria [25]. Baseline data including demographic, clinical, and treatment profile were collected by review of patients' electronic medical record retrospectively.

All electronic records in RA patients were screened whether diagnosis of VTE had been documented with the Text Mining procedure. In this study, the use of text mining enabled automatic extraction of potential candidate signs and symptoms of thrombosis from clinical narratives and could extract candidate patients with less omissions than extraction based on disease name only. The presence of VTE was confirmed by venous ultrasound and/or enhanced computed tomography (CT) in all VTE patients. In this study, VTE group was defined as RA patients who developed a first episode of VTE during the observation period. Patients with a history of VTE prior to the observation period or those who received antithrombotic agents for any reason during the observation period were excluded from the study.

To evaluate the risk factors for development of VTE in RA, we selected 10 RA patients

per case as control group using density sampling from all at-risk patients who did not experience thrombotic events at the time as cases occur.

Variables

Hypertension was defined as use of any antihypertensive medication or blood pressure higher than 140/90 mmHg on more than two occasions during the follow-up period [26]. Diabetes mellitus (DM) was defined as use of any antidiabetic medication or serum haemoglobin A1c >6.5% [27]. Dyslipidaemia (DLp) was documented if the patient had at least one of the following: use of any lipid-lowering agents, serum low-density lipoprotein concentration >140 mg/dL, high-density lipoprotein concentration < 40 mg/dL, or triglyceride >150 mg/dL [28, 29]. Patients were classified as having chronic kidney disease if their estimated glomerular filtration rate was < 45 mL/min at any visit [30]. Rheumatoid arthritis-associated lung disease (RA-LD) was defined as interstitial lung disease (ILD), bronchiectasis, or pleural disease diagnosed by chest X-ray or CT scan [31]. Current or past smoking of a total of 10 pack-years or more was documented as a positive smoking history [32].

Assessment of disease activity

DAS28ESR/CRP were collected at baseline and every year until the patient developed VTE or when the patient's record was censored. These measures consisted of 28-tender joint count (TJC28), 28-swollen joint count (SJC28), ESR, CRP, and the patient's global assessment of disease-related general health on a visual analogue scale (PGA). When there was insufficient data to calculate DAS28ESR/CRP at the time of the visit one year after the last measurement, DAS28ESR/CRP score was documented according to the last observation carrying forward procedure. To investigate the effect of

the level of inflammation over time, we calculated time-averaged DAS28CRP. It was obtained by calculating the area under the curve of the DAS28CRP score measured during the observation period (each year) and dividing it by total observation years. (19)

Statistical analysis

Categorical variables were described as counts and percentages. Data normality was checked by graphically and the Shapiro-Wilk test. Based on the results of normality test, all continuous variables (age, disease duration, body mass index [BMI], drug dosage, DAS28ESR/CRP, and time-averaged DAS28CRP) were expressed as median and quartiles. Non-parametric tests were used for comparisons. Univariate conditional logistic regression analysis was used to assess the significant factors associated with VTE and to calculate the odds ratio (OR). Conditional multivariate logistic-regression model was created to identify independent predictors of development of VTE, which was considered as a dependent variable. The selection of independent variables was based on results of univariate analysis and reviewing previous literature. Before multivariate logistic regression analysis, bivariate correlations between variables were checked to verify that there was no potential multicollinearity. The adjusted odds-ratio (OR) associated with each potential risk factor and the 95% confidence interval (CI) were calculated with conditional logistic regression analysis. Cut-off levels of the time-averaged DAS28CRP was defined to maximize Youden Index with sensitivity of more than 70% using ROC curve. Screening performance of this factor was expressed as area under ROC curve (AUC), sensitivity, and specificity. We considered the AUC as acceptable if it is between 0.7 and 0.9 and excellent if >0.9. In all statistical analyses, $p < 0.05$ was considered statistically significant. All statistical analyses were performed using JMP® Pro 14.2.0

(SAS Institute Inc., Cary, North Carolina, USA).

Results

Patients' characteristics

A total of 1,379 RA patients were identified in this study. Seventy-eight percent were female (N= 1076) and median age at diagnosis was 54 years [first quartile to third quartile (Q1-Q3) 42-64]. Of these subjects, 28 patients developed VTE, but two were excluded because of previous episodes, and one of the two patients with previous thrombotic episodes had been received anticoagulation for cardiac disease. 26 patients were included in VTE group, and the median age at the time of diagnosis of VTE was 74 years (Q1-Q3 64-79) (Table 2). The most common site of VTE was in the lower extremities, and the most frequent symptom was oedema. Oedema itself was the most common reason for hospitalization, followed by infection and orthopaedic operation. In the VTE group, there were no patients with paraplegia or protein C/S deficiency, which are known risk factors for thrombosis (Table 1).

Comparisons of clinical characteristics between patients with and without VTE

To evaluate the risk factors for the development of VTE, 10 controls for each case were selected using density sampling among the enrolled RA patients without VTE and 260 cases were assigned as control (non-VTE) group (Figure 1) (Table 2). Of the 1351 patients in non-VTE group, 61 patients were on anticoagulant therapy for cardiac disease. The patients who were already on anticoagulation were excluded before selection using density sampling. There were no statistically significant differences between patients in VTE group and those in non-VTE group in RA duration, history of hospitalisation, orthopaedic and other operation, and malignancy. However, age, body

mass index (BMI), presence of DM, RA-LD and glucocorticoid usage were identified as potential risk factors of VTE by univariate analysis. Furthermore, time-averaged DAS28CRP was significantly associated with development of VTE (Table 2). In multivariate logistic regression analysis, age and time-averaged DAS28 were identified as significant risk factors for the development of VTE in RA patients (Table 3).

Associations between time-averaged DAS28CRP and VTE development based on ROC curve analysis

We defined cut-off levels of the time-averaged DAS28CRP to maximize Youden Index with sensitivity of more than 70% using ROC curve. ROC analysis showed that the AUC for time-averaged DAS28CRP as a predictor for VTE development was 0.78. The optimal cut-off point for time-averaged DAS28CRP was 2.7 with 78% sensitivity and 72% specificity (Figure 2).

Discussion

This case control study revealed that high disease activity over time was associated with development of VTE in our population with RA.

There have been few previous studies on the relationship between RA disease activity and development of thrombosis, although a number of studies have shown that probability of having VTE is higher in patients with RA compared to the general population [11-14, 33]. Recently, Molander V, et al. [22] performed a nation-wide cohort study to investigate the association of clinical RA disease activity with risk of having VTE. This big-data study consisting of a total of 322,601 visits by 46,316 RA patients during 2006 to 2017 revealed that higher disease activity, as measured by DAS28, was associated with an increased risk of thrombosis. However, the use of DAS28 at one-point as a measure of disease activity could lead to misinterpretation of true RA disease activity, as comorbidities that cause elevated CRP or ESR, may contribute to the DAS28 score. Since the subsequent course of the score also varies with differences in treatment response, a single DAS28 could not reflect the overall disease activity of patients during the observation period. Our single centre study was smaller than the one held in Sweden, although we were able to collect vastly precise and detailed clinical information from the patients' record. In particular, we could show the correlation between thrombosis development and disease activity measured throughout the follow-up period in each patient. Time-averaged DAS28CRP would be more valuable to assess the overall disease activity in a given RA patient than a single determination of DAS28, since the average was less affected by the transient elevation of serum CRP levels due to the events other than elevation in RA activity, including infectious diseases, fractures or surgical

operation. Patients with higher time-averaged DAS28 was associated with development of VTE compared to those without VTE significantly, indicating that chronic inflammatory procedure due to RA over time plays a role in development of thrombosis. Moreover, results of the ROC analysis suggested that obtaining remission is critical not only for preventing joint destruction but also for reducing risk to have VTE events.

Venous stasis, one of the components of Virchow's triad, is considered to be related with prolonged surgical operations, prolonged immobility such as hospitalization, and varicose veins. Especially, since Total knee replacement (TKR) and total hip replacement (THR) are strongly associated with the development of thrombosis, we performed a sensitivity analysis by excluding 3 patients who received TKR or THR and 30 matched controls、and the results were the same as before the exclusion. In addition, we found no patients with known risks of paraplegia or taking oral contraceptives or hormone replacement therapy. Chronic inflammation also has been shown to be related with vascular endothelial damage and upregulated coagulation among the three factors listed in the Virchow's triad [3-7]. Venous stasis may also be present in RA patients with high disease activity because limited mobility and synovial effusion can affect blood flow. Control of disease activity could ameliorate these thrombosis-prone abnormalities.

In addition, it is unclear whether the results of this large cohort are independent of racial differences because the incidence of thrombosis is generally lower in Asians than in Caucasians probably due to differences in genetic backgrounds [34, 35]. Indeed, the incidence of VTE was 5.9 per 1000 person-years in another Swedish cohort [14], 1.3 per 1000 person-years in Taiwan [11] and 2.7 per 1000 person-years in our data (data not shown). On the other hand, the association between RA disease activity and occurrence

of VTE in our data are consistent with that observed in the Swedish study, suggesting that high disease activity may contribute greatly to the development of VTE in RA patients regardless of racial difference.

There are some important limitations to be considered in this study. Firstly, due to the retrospective study design, obtaining patient data were restricted to their medical record review. There was insufficient information on suggestive of predispositions to thrombosis, such as family history, and the presence of protein C/S deficiency or antiphospholipid antibodies in some of the patients leading to be incapable of evaluating the effects of these and other potential confounding factors.

Secondly, not all patients had VTE screening and patients with asymptomatic or minimal symptomatic VTE might not be included. Thirdly, this study was performed only in the Japanese population in which genetical risk factors for occurrence of thrombosis would be different from those in the European population. Thus, results of our study should be confirmed in a different population.

In conclusion, the present study describes the association between persistence of RA disease activity and development of VTE, suggesting that sustained achievement of clinical remission could be beneficial for decrease the risk of VTE.

Statement on open data sharing Data sharing is not applicable due to ethical restrictions.

Availability of data and materials The data that support the findings of this study will be available from the corresponding author upon reasonable request.

Declarations/Ethical approval This study and protocol were conducted in accordance with the ethical principles of Declaration of Helsinki and the Good Clinical Practice guidelines approved by Hokkaido University Hospital Ethics Committee (approval number: 020-0072). Date: 6/11/2020.

Informed consent This study is a retrospective study. Patients were not required to give informed consent to this particular study because the analysis used anonymous clinical data that were obtained patients who had given prior written consent. We also applied an Opt-out method to obtain consent on this study.

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Figure legend

Fig. 1 Flow of the study selection

In the population of 1,379 RA patients who visited our hospital with greater than 2-years follow up from January 2010 to June 2019, a total of 28 cases diagnosed with VTE were identified. Two cases were excluded due to the history of VTE before observation period. The remaining 26 cases were included as VTE group. In terms of control group, 260 cases were extracted by density sampling at the time cases occur.

Fig. 2 Receiver operating characteristic (ROC) curves with area under the curve (AUC) for time-averaged DAS28CRP

Cut-off levels of the time averaged DAS28CRP was defined to maximize Youden Index with sensitivity of more than 70% using ROC curve. The sensitivity and specificity were 78 % and 72 %, respectively. The AUC of the model was 0.78.

Table1. Profiles of venous thromboembolism (VTE) patients

	N= 26
Site of occurrence	
Lower extremity	24 (92 %)
Upper extremity	2 (8 %)
Lung	4 (15 %)
Modality of diagnosis	
Ultrasonography	13 (50 %)
Enhanced CT	13 (50 %)
Symptoms/Laboratory Findings suggesting VTE	
D-dimer elevation	13 (50 %)
Edema	8 (32 %)
Dyspnea	3 (12 %)
Others	3 (12 %)
Onset during hospitalization	22 (85 %)
Reason for hospitalization	
Oedema (VTE itself)	6 (23 %)
Infection	5 (20 %)
Orthopedic surgery	3 (12 %)
Dyspnea	2 (8 %)
Malignancy	1 (4 %)
Presence of aPL (N= 14 tested)	1 (7 %)
Presence of PS (N=10 tested)	0 (0%)
Presence of PC (N=11 tested)	0 (0%)

Binary values are number (percent) unless otherwise indicated.

CT: Computed tomography, aPL: antiphospholipid antibodies, PS: Protein S, PC: Protein C

Table2. Characteristics in RA patients with or without venous thromboembolism (VTE).

Factors	VTE (n=26)	Non-VTE (n=260)	OR (95%CI)	P value
Age (median, [Q1-Q3])	74.5 (63.8-79.3)	64.5 (55.0-73.0)	1.08 (1.04-1.14)	<0.0001*
Follow-up period (week) (median, [Q1-Q3])	203.0 (87.3-75.0)	197.0 (104.5-366.8)	0.99 (0.99-1.00)	0.200
Female, No. (%)	21 (80.8)	209 (80.4)	1.01 (0.63-1.77)	0.963
Past or current smoking, No. (%)	7 (33.3)	64 (38.6)	1.06 (0.65-1.65)	0.795
Bone erosions on X-ray, No. (%)	18 (78.3)	153 (64.0)	1.25 (0.82-1.98)	0.301
RA duration (year) (median, [Q1-Q3])	9.0 (2.8-18.0)	10.0 (6.0-17.0)	1.00 (0.96-1.03)	0.904
RF, No. (%)	24 (92.3)	188 (72.9)	2.14 (1.15-5.39)	0.013*
ACPA, No. (%)	15 (78.9)	162 (76.1)	0.91 (0.60-1.39)	0.644

BMI (kg/ m^2) (median, [Q1-Q3])	25.7 (21.6-27.6)	21.9 (19.7-24.2)	1.17 (1.06-1.31)	0.001*
History of hospitalization, No. (%)	15 (57.6)	113 (43.5)	1.34 (0.89-2.06)	0.159
History of orthopedic surgery, No. (%)	3 (12.0)	43 (16.5)	0.81 (0.39-1.41)	0.494
History of other surgery, No. (%)	0 (0.0)	20 (7.8)	0.47 (0.04-1.30)	0.081
Complications				
DM, No. (%)	12 (46.2)	59 (23.5)	1.69 (1.11-2.54)	0.014*
DLp, No. (%)	7 (26.9)	112 (44.1)	0.70 (0.43-1.07)	0.105
CKD, No. (%)	9 (34.6)	59 (22.7)	1.32 (0.85-1.99)	0.201
RA-LD, No. (%)	10 (38.5)	34 (13.3)	2.10 (1.33-3.30)	0.002*
HT, No. (%)	10 (38.5)	102 (39.8)	0.98 (0.64-1.47)	0.939
Malignancy, No. (%)	3 (11.5)	39 (15.0)	0.86 (0.41-1.50)	0.653
Treatment				
PSL use, No. (%)	20 (76.9)	113 (43.5)	2.09 (1.34-3.51)	0.001*
MTX use, No. (%)	13 (50.0)	144 (55.4)	0.90 (0.60-1.35)	0.598
SASP use, No. (%)	5 (19.2)	54 (20.8)	0.95 (0.55-1.52)	0.855
TNFi use, No. (%)	7 (26.9)	41 (15.8)	1.38 (0.85-2.14)	0.179
TCZ use, No. (%)	0 (0.0)	23 (9.0)	0.44 (0.04-1.21)	0.058
ABT use, No. (%)	1 (3.8)	18 (7.0)	0.73 (0.17-1.67)	0.518
JAKi use, No. (%)	2 (7.7)	15 (5.8)	1.17 (0.46-2.24)	0.707
NSAIDs use, No. (%)	5 (19.2)	56 (21.5)	0.93 (0.53-1.49)	0.785
Celecoxib use, No. (%)	1 (4.0)	28 (10.8)	0.57 (0.13-1.29)	0.209
RA disease activity				
Time-averaged DAS28CRP, (median, [Q1-Q3])	3.2 (2.6-4.5)	2.2 (1.7-2.8)	3.25 (1.94-6.12)	<0.0001*
DAS28CRP, (median, [Q1-Q3])	3.1 (2.5-4.2)	2.0 (1.4-3.0)	1.66 (1.04-2.71)	0.03*
DAS28ESR, (median, [Q1-Q3])	4.0 (2.3-5.2)	2.8 (2.0-3.6)	1.63 (1.05-2.60)	0.03*

Continuous values are the median (25 percentile - 75 percentile). Binary values are number (percent) unless otherwise indicated.

* Conditional logistic regression model, significance at $P<0.05$

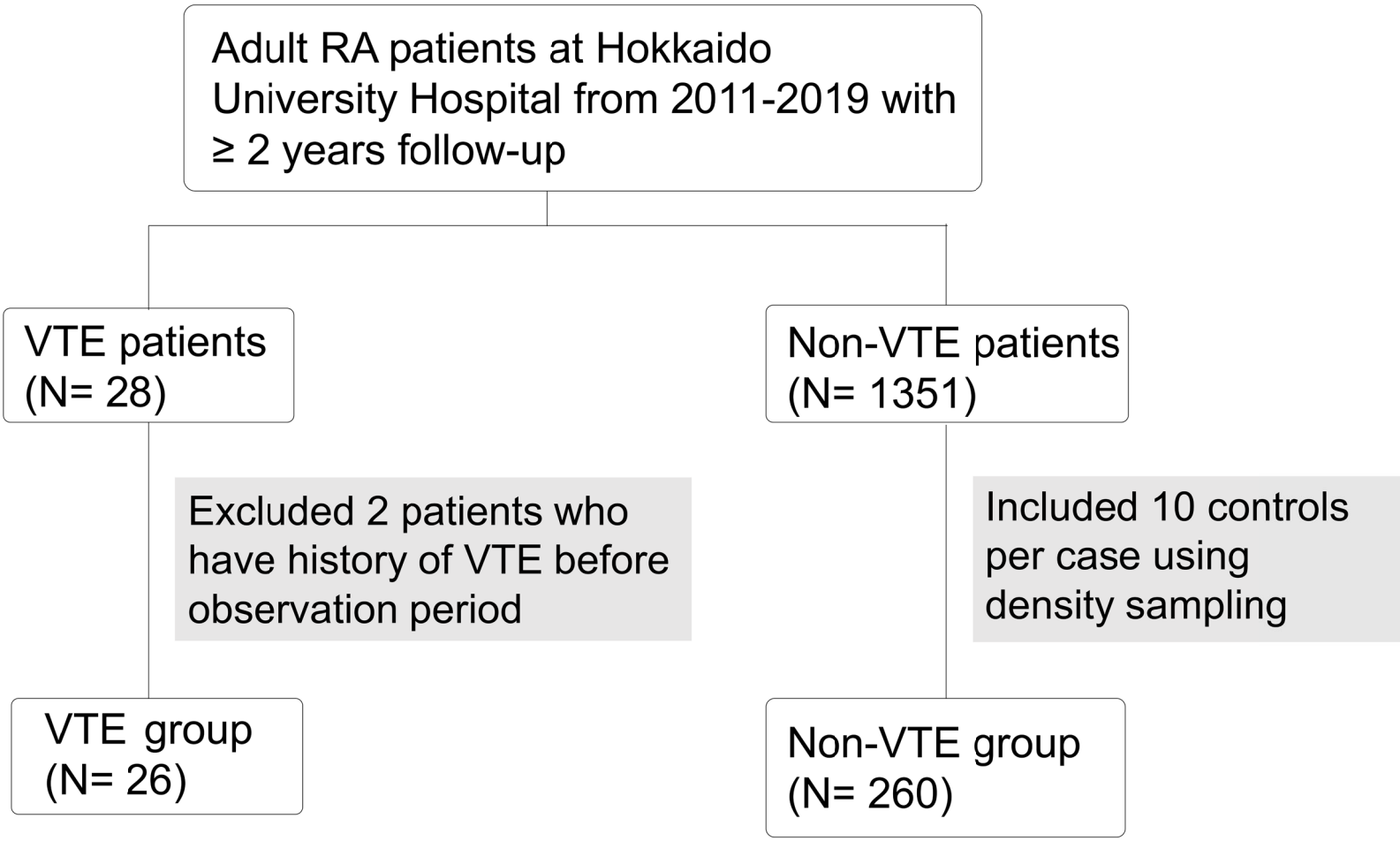
No.: Number, Q1-Q3: first quartile to third quartile, OR: odds ratio, 95%CI: 95% confidence interval, RA: Rheumatoid arthritis, RF: Rheumatoid factor, ACPA: anti-cyclic citrullinated peptide antibody, BMI: Body mass index, DM: Diabetes mellitus, DLp: Dyslipidemia, CKD: Chronic kidney disease, RA-LD: Rheumatoid arthritis-associated lung disease, HT: Hypertension, PSL: Prednisolone, MTX: Methotrexate, SASP: Salazosulfapyridine, TNFi: Tumor Necrosis Factor inhibitors, TCZ: Tocilizumab, ABT: Abatacept, JAKi: Janus kinase inhibitors, NSAIDs: Non-steroidal anti-inflammatory drugs, DAS28:

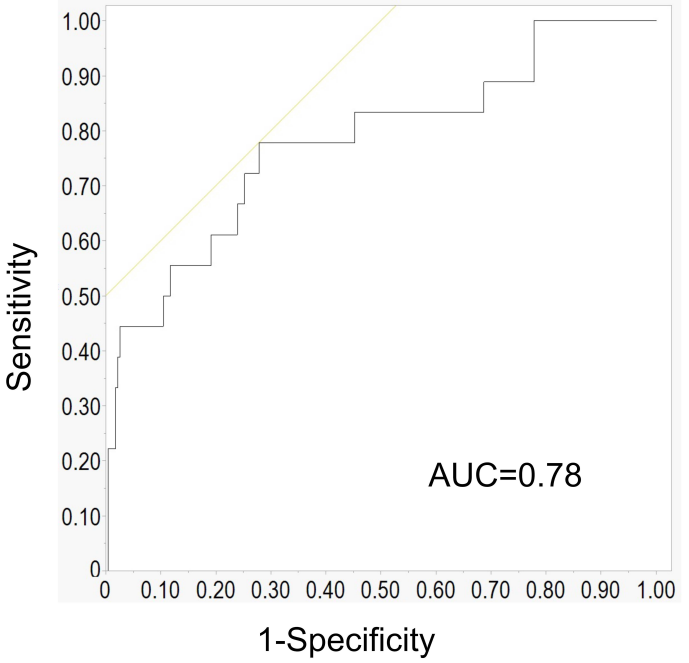
Disease Activity Score28, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein,

Table3. Multivariate logistic regression analysis

Items	Estimate	SE	aOR	95%CI	P value
Age	0.08	0.03	1.09	1.03-1.12	0.003*
BMI	0.12	0.07	1.12	0.99-1.31	0.072
Time-averaged DAS28CRP	1.22	0.37	3.40	1.77-7.85	0.0001*

SE: Standard error, aOR: adjusted odds ratio, 95%CI: 95% confidence interval, BMI: Body mass index, PSL: Prednisolone, DAS28: Disease Activity Score28


Adult RA patients at Hokkaido University Hospital from 2011-2019 with ≥ 2 years follow-up
VTE patients (N= 28)
Non-VTE patients (N= 1351)
Excluded 2 patients who have history of VTE before observation period
Included 10 controls per case using density sampling
VTE group (N= 26)
Non-VTE group (N= 260)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0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0
0
0.10
0.20
0.30
0.40
0.50
0.60
0.70
0.80
0.90
1.00
1-Specificity
AUC=0.78