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Evaluation of the efficacy of anticoagulation therapy in reducing mortality in a nationwide cohort of hospitalized patients with coronavirus disease in Japan

Hisao Hara^{a,*}, Yukari Uemura^b, Kayoko Hayakawa^{c,d}, Tomiteru Togano^e, Yusuke Asai^d, Nobuaki Matsunaga^d, Mari Terada^{b,c}, Hiroshi Ohtsu^b, Koji Kitajima^b, Yousuke Shimizu^b, Lubna Sato^c, Masahiro Ishikane^{c,d}, Noriko Kinoshita-Iwamoto^{c,d}, Taro Shibata^f, Masashi Kondo^g, Kazuo Izumi^b, Wataru Sugiura^f, Norio Ohmagari^{e,f}

^a Department of Cardiology, National Centre for Global Health and Medicine, Tokyo, Japan

^b Biostatistics Section, Centre for Clinical Sciences, National Centre for Global Health and Medicine, Tokyo, Japan

^c Disease Control and Prevention Centre, National Centre for Global Health and Medicine, Tokyo, Japan

^d AMR Clinical Reference Centre, National Centre for Global Health and Medicine, Tokyo, Japan

^e Department of Haematology, National Centre for Global Health and Medicine, Tokyo, Japan

^f Biostatistics Division, Centre for Research Administration and Support, National Cancer Centre, Tokyo, Japan

^g Centre for Clinical Trial and Research Support, Fujita Health University, Aichi, Japan

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ABSTRACT

Objectives: To determine whether anticoagulation therapy improves outcomes in patients with coronavirus disease 2019 (COVID-19) in Japan given their lower risk of thrombosis compared with Western cohorts.

Methods: The efficacy of anticoagulation therapy in hospitalized patients with COVID-19 was evaluated using a nationwide registry: the COVID-19 Registry Japan. The inverse probability of weight treatment method was used to adjust for baseline confounders in the anticoagulation and non-anticoagulation groups.

Results: Of the 1748 patients included, anticoagulants were used in 367 patients (treatment group). The patients in the anticoagulant group were older, predominantly male, and often presented with obesity, hyperlipidaemia, hypertension, diabetes and elevated D-dimer levels. Twenty-nine-day mortality was 7.6% in the whole cohort (treatment group, 11.2%; no treatment group, 6.6%), 6% in patients who were not treated with steroids (treatment group, 12.3%; no treatment group, 5.2%), and 11.2% in patients treated with steroids (treatment group, 10.5%; no treatment group, 11.8%). Mortality in the whole cohort was similar between the treatment and no treatment groups (P=0.99), and an insignificant decreasing trend in mortality was observed in patients treated with steroids (P=0.075).

Conclusions: Anticoagulants may be beneficial in Asians, in whom comorbidities and risk of thrombosis may differ from other ethnic groups.

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Introduction

Globally, coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has

E-mail address: hhara@hosp.ncgm.go.jp (H. Hara).

affected more than 120 million individuals and caused 2.7 million deaths (Roser et al., 2021). As of 23 March 2021, there have been 457,754 cases and 8861 deaths in Japan (Ministry of Health, Labour and Welfare, 2021), which is lower than the number of cases and deaths reported in other countries with outbreaks of COVID-19 (Roser et al., 2021).

Thromboembolism, in addition to inflammation, has been reported to be associated with severe SARS-CoV-2 infection (McBane et al., 2020). Despite controversy regarding appropriate



^{*} Corresponding author. Department of Cardiology, National Centre for Global Health and Medicine, 1-12-1 Toyama Shinjuku-ku, Tokyo 162-8655, Japan. Tel.: +81 3 3202 7181; fax: +81 3 3202 7364.

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dosing (i.e. prophylactic vs treatment dosing), several studies have shown that the use of anticoagulants, such as heparin, could cause a reduction in mortality and intubation in patients hospitalized for COVID-19 (Rentsch et al., 2019; Hanif et al., 2020; Nadkarni et al., 2020), leading to recommendations for their use in treatment guidelines (Cuker et al., 2021; National Institutes of Health 2021a).

In contrast, previous studies have shown that patients with COVID-19 in Japan have a lower prevalence of underlying diseases, such as diabetes and obesity, which are associated with the severity of COVID-19, compared with patients in Western countries (Matsunaga et al., 2020). In addition, the risk of developing venous thromboembolism is lower in Asians than in Caucasians due to genetic differences (Nicole Tran and Klatsky, 2019).

There is a need to investigate whether anticoagulants have the same effect on COVID-19 in Japanese patients as in other ethnic groups. However, to the best of the authors' knowledge, there have been no large-scale reports on this topic. As such, this study was undertaken to investigate the efficacy of anticoagulants in reducing mortality using COVID-Registry Japan (COVIREGI-JP), a nationwide cohort of hospitalized patients.

Methods

Study design and data

This study used data from COVIREGI-JP (Matsunaga et al., 2020). The inclusion criteria for enrolment were: (1) a positive SARS-COV-2 test result; and (2) inpatient treatment at a healthcare facility.

The case report form of the International Severe Acute Respiratory and Emerging Infection Consortium was modified for the collection of clinical epidemiological information and treatment data in Japan (ISARIC, 2021). Information on the use of anticoagulation therapy, including unfractionated heparin, low-molecularweight heparin, fondaparinux and oral anticoagulants [warfarin, direct oral anticoagulants (dabigatran, rivaroxaban, apixaban and edoxaban)] during hospitalization was collected. This study did not distinguish between prophylactic and therapeutic administration for thromboembolism.

Study data were collected and managed using Research Electronic Data Capture, a secure, web-based data capture application hosted at the JCRAC data centre of the National Centre for Global Health and Medicine (Harris et al., 2009).

Data used were from cases that contained information on all of the major items, as of 2 November 2020, as described in a previous report (Matsunaga et al., 2020).

Population for analysis

Among all patients registered as COVID-19 cases in COVIREGI-JP, the following were excluded:

- those who received antiplatelet and/or anticoagulation therapy prior to the study (the new user approach was employed to avoid bias introduced by the inclusion of prevalent users in the study cohort);
- those who died within 4 days of admission to hospital (to exclude those who were already in a severe condition, to facilitate effective evaluation of treatment efficacy); and
- those who were categorized as 'severe' (i.e. invasive or non-invasive mechanical ventilation, requiring supplemental oxygen, SpO₂ ≤94% on room air or tachypnoea (respiratory rate ≥24 breaths per min)] at the time of admission (to exclude patients who were already severely ill at admission, and thus were less likely to show clinical benefit from anticoagulation therapy thereafter) (Beigel et al., 2020; Matsunaga et al., 2020).

Statistical analyses

The inverse probability of treatment weight (IPTW) method was used to adjust for baseline confounders. IPTW creates a pseudopopulation in which all participants are considered conditionally exchangeable by achieving a balance between the treated and non-treated groups on the baseline covariates. The weight for each participant is defined as the inverse of the probability of receiving the observed treatment conditional upon the baseline covariate. That is, the weight of each patient receiving the anticoagulant drug is the inverse of the probability of receiving the drug [propensity score (PS)], whereas the weight of a patient not receiving the anticoagulant drug is the inverse of 1-PS. PS was estimated using multi-variable logistic regression models, including the baseline variables in the model, which are listed in Table 1. The association between anticoagulant drug administration and 29-day mortality was estimated using the IPTW of the marginal structural Cox model. Similarly, the associations between the administration of an anticoagulant drug and overall death were estimated for patients who received steroid treatment and those who did not receive steroid treatment during admission. The subgroup-specific PS model was used to account for the differences between the steroid and no steroid treatment groups. Time-varying confounding factors were not adjusted because the timing of anticoagulant prescription was not observed. Missing values were imputed using the mean values for continuous variables and median values for categorical variables. All statistical analyses were performed using SAS Version 9.4 (SAS Institute, Cary, NC, USA).

Ethical approval

This study was approved by NCGM Ethics Review Board (NCGM-G-003494-0).

Results

Of the 8912 patients, 1748 patients did not meet the exclusion criteria and were included in the study (anticoagulation treatment group, n=367; non-treatment group, n=1381). Table 1 shows the differences in background characteristics according to whether or not the patients were treated with anticoagulants during hospitalization. The patients in the treated group were older, predominantly male, had a higher body mass index (BMI), and had a higher D-dimer level at admission. Hypertension, hyperlipidaemia, diabetes and obesity (as diagnosed by a physician) were more common in the treatment group than in the non-treatment group. The use of angiotensin II receptor blockers (ARBs) before hospitalization was more common in the treatment group. After adjustment for multi-variate models to generate PS, most of these variables were still significantly different between the two groups, although the differences in obesity and use of ARBs disappeared. A significant difference in dementia was observed after adjustment.

Figure 1 summarizes the survival probability by day 29 in patients who received and did not receive anticoagulation therapy during hospitalization. The results are presented for three groups: whole cohort (Figure 1a), patients who did not receive steroids (Figure 1b), and patients who received steroids (Figure 1c).

In the whole cohort, the survival probability tended to decrease more in the anticoagulant group after approximately 15 days of hospitalization. A stratified analysis according to the presence or absence of steroid use during hospitalization showed that the survival probability among patients who did not receive steroids in the anticoagulant group tended to be lower than that in the non-anticoagulant group from day 5 after hospitalization, and this trend continued until day 29. In contrast, in patients who received steroids, the survival probability in the non-anticoagulant group

Table 1

Characteristics of patients with or without anticoagulation treatment during hospitalization.

Age, years Mean (SD) 55.3 (21.7) 65.3 (21.7) 67.3 (24.1)			No treatment (<i>n</i> =1381) <i>n</i> (%)	Treatment (<i>n</i> =367) <i>n</i> (%)	OR (95% CI)	P-value ^a	Adjusted OR (95% CI)	<i>P</i> -value ^a
Media (1QR) 67 (48-7) 67 (5-76) 1.0 (1, 10-1.102) -0.000 1.02 (1, 10-1.03) -0.0001 BML, % Mean (10) 24 5 (4.7) 26 (2.1) 26 (2.1) -0.0001 1.05 (1, 02-1.08) 0.0001 Deliner Media (100) 0.05 (10, 00-0.05) 0.7 (00016-1.4) 1.06 (1, 04-1.99) -0.0001 1.05 (1, 02-1.08) 0.0001 Days from disease 0000 Median (100) 0.05 (10, 00-0.05) 0.7 (00016-1.4) 1.10 (10, 01-1.4) -0.001 1.07 (1, 03-1.12) 0.010 Marking alcohol Currentstatistankow 7.3 (8.33) 1.36 (4.31.5) 0.17 (1, 03-1.12) 0.010 Myscardal Infarction Ves 88 (655) 2.47 (7.73) 1.11 (0.87-1.41) 0.44 0.96 (0.75-1.26) 0.9320 Myscardal Infarction Ves 49 (3.55) 1.27 (1.33) 1.37 (0.43-434) 0.584 0.99 (0.29-3.45) 0.9320 Myscardal Infarction Ves 67 (4.35) 1.05 (1.41) 1.37 (0.43-434) 0.584 0.99 (0.29-3.45) 0.9320 Myscardal Infarction Ves 77 (4.15) <	Age, years	Mean (SD)	59.3 (21.7)	65.3 (14.1)				
Sex MM. 7. Male 876 (63.47) Median (108) 245 (47) 245 (31) 26 (5.1) 0.001 5.87 (1.2~1.58) 0.0017 Median (108) 245 (4.7) 26 (3.1) 0.011 (1.4-1.68) -0.001 1.05 (1.02-1.08) 0.0004 Days from disease onset Mean (207) 64 (6.5) 7.4 (4.5) 1.10 (1.04-1.14) -0.000 1.07 (1.03-1.12) 0.011 Smoking history Currentpast smoke 537 (38.59) 158 (43.13) 1.13 (0.44-15) 0.144 0.96 (0.75-1.26) 0.732 Diraking alcond Yes 8 (0.63) 2.(0.73) 0.84 (0.2-4.45) 0.932 0.07 (1-0.15) 0.148 Congersive harcing law Yes 4 (1.25) 10 (2.73) 0.84 (0.2-4.45) 0.932 0.72 (0.36-1.42) 0.333 Morarial Yes 11 (0.87) 4 (1.13) 1.73 (0.47-4.34) 0.54 (0.2-4.54) 0.592 Cerebrowscular disease Yes 11 (0.81) 4 (1.13) 0.97 (0.47-4.34) 0.54 (0.2-4.54) 0.527 Cerebrowscular disease Yes 11 (0.81) 19 (0.233) 0.63 (0.3-2.23)		Median (IQR)	62 (48-75)	67 (56-76)	1.02 (1.01-1.02)	< 0.0001	1.02 (1.01-1.03)	< 0.0001
bms. Mean (SD) 24.5 (4.7) 26 (3.1) D-dimer Mean (SD) 0.0 (2.4) 1.6 (2.3) 1.0 (1.04-1.09) -0.0001 1.07 (1.03-1.12) 0.0001 Days from disease one Moon (SD) 6.4 (4.9) 7.4 (6.4) 1.10 (1.05-1.14) 1.00 (1.05-1.02) 0.01 (0.07-1.28) 0.014 Days from disease one Modian (QK) 6.4 (9.9) 7.4 (4.5) 1.10 (0.10-1.14) 0.001 0.012-1.28) 0.031 Sindiar Jackon Vers 8.98 (6.53) 2.4 (7.67.33) 1.11 (0.87-1.14) 0.44 0.96 (0.75-1.28) 0.932 Mycaradal infarction Vers 4.8 (0.8) 2.4 (0.73) 1.11 (0.87-1.41) 0.44 0.96 (0.75-1.28) 0.932 Congorstive start failure Vers 4.4 (1.27) 10 (2.7 (7.3)) 0.32 (0.24-1.31) 0.932 0.72 (0.36-1.42) 0.932 Perspheral vascular disase Vers 1.1 (0.87) 4 (1.13) 0.94 (0.23-3.42) 0.9492 Paralysis Vers 1.1 (0.87) 1.6 (1.25,1) 0.05 (0.23-1.42) 0.923 (0.23-1.42) 0.924	Sex	Male	876 (63.4%)	264 (71.9%)	1.48 (1.15-1.9)	0.0025	1.62 (1.2-2.19)	0.0017
Median (0R) 249 (21 - 23.3) 25 (2.1 - 23.0) 1.05 (1.04 - 1.09) -0.001 1.05 (1.02 - 1.08.) 0.000 Days from disease one Mean (TQS) 0.05 (0.02 - 0.05) 0.7 (0.0016 - 1.1) 1.10 (1.05 - 1.14) -0.001 1.07 (1.03 - 1.12) 0.011 Smoking history Carrenepsast smake 537 (28.5%) 74 (6.4) 1.02 (1.04 - 1.05) 0.144 0.90 (7.6 - 1.28) 0.5723 Dimking allows Ves 8 (0.63) 2 (0.53) 0.94 (0.2 - 4.3) 0.930 0.772 - 1.26) 0.5733 Opcompating discase Ves 4 (3.25) 10 (2.75) 0.58 (0.42 - 1.71) 0.590 0.75 (0.36 - 1.42) 0.3339 Infarction (ongestiv Ves 4 (3.25) 10 (2.75) 0.58 (0.42 - 1.03) 0.990 0.72 (0.36 - 1.22) 0.3239 Infarction (ongestiv) Ves 4 (3.25) 10 (2.75) 0.58 (0.42 - 1.30) 0.990 0.72 (0.36 - 1.22) 0.3239 Infarction (ongestiv) Ves 4 (3.25) 10 (2.75) 0.70 (0.4 - 4.31) 0.990 0.53 (0.32 - 3.42) 0.990 Carcenovascating disease	BMI, %	Mean (SD)	24.5 (4.7)	26 (5.1)				
D-dimer Mean (SD) 0.9 (2.4) 16 (3) Hand IIQ8N 6.56 (0.00–0.58) 0.7 (0.0016-1.4) 1.02 (1.00–1.4) 0.0027 1.01 (1-1.03) 0.1136 Byn from dinease onset Mean (VQR) 6.4 (6.9) 7.4 (4.9) 1.02 (1.00–1.44) 0.029 0.011 0.911 Sinaking Linour Communication (VQR) 6.1 (0.8) 1.7 (4.9.5) 1.01 (1-1.03) 0.914 <td></td> <td>Median (IQR)</td> <td>24.9 (21.9-26.3)</td> <td>26 (23.1-28.0)</td> <td>1.06 (1.04-1.09)</td> <td>< 0.0001</td> <td>1.05 (1.02-1.08)</td> <td>0.0004</td>		Median (IQR)	24.9 (21.9-26.3)	26 (23.1-28.0)	1.06 (1.04-1.09)	< 0.0001	1.05 (1.02-1.08)	0.0004
Median (108) 6.56 (0.00-0.56) 0.77 (0.0016-1.4) 1.10 (1.05-1.14) 0.0000 1.07 (1.03-1.12) 0.010 Days from discasement Gamma (150) 6.54 (6.9) 7.4 (4.9.5) 1.10 (1.05-1.41) 0.0100 1.01 (1-1.03) 0.1136 Sonsking history Currently ast mode Sist (4.3.13) 1.19 (0.04-1.5) 0.124 0.090 (0.05-1.26) 0.7340 Comparison Ves 888 (635) 247 (77.33) 1.11 (0.87-1.41) 0.65 (0.02-1.26) 0.7393 Mycardial Ves 49 (3.55) 10 (2.73) 1.11 (0.87-1.41) 0.65 (0.02-1.26) 0.3393 Infarcting/congerive Ves 11 (0.83) 4 (1.13) 1.37 (0.43-434) 0.5894 0.99 (0.29-3.45) 0.9922 Cerebroxscular disease Ves 11 (0.83) 4 (1.13) 0.40 (0.33-1.81) 0.51 (0.32-2.42) 0.291 (0.29-3.45) 0.9922 Cerebroxscular disease Ves 11 (0.83) 16 (1.25) 4 (1.13) 0.26 (0.33-1.61) 0.51 (0.32-2.42) 0.291 (0.29-3.45) 0.291 (0.29-3.45) Darabity ing dinear Ves 11 (1.8	D-dimer	Mean (SD)	0.9 (2.4)	1.6 (3)				
Days from disease enset Mean (Sb) 6.4 (6.9) 7.4 (6.4) Smoking listory Current/past smoker 537 (3.8.3) 158 (43.13) 1.19 (0.94-1.5) 0.0174 0.0472 0.01 (1-1.03) 0.91 (2.0.91) Diriking Jobbel Yes 8 (0.53) 247 (67.37) 1.01 (0.71-41) 0.4142 0.039 (0.73-1.28) 0.91 (2.0.91) Mycantall inferction Yes 40 (3.25) 1.01 (2.71-41) 0.4142 0.039 (0.73-1.28) 0.739 (0.71-41) 0.4142 0.039 (0.71-128) 0.739 (0.71-41) 0.4142 0.039 (0.21-31) 0.039 (0.21-31) 0.039 (0.21-31) 0.039 (0.21-31) 0.039 (0.21-31) 0.039 (0.21-31) 0.039 (0.21-31) 0.039 (0.21-31) 0.039 (0.21-31) 0.039 (0.21-31) 0.039 (0.21-31) 0.039 (0.21-31) 0.039 (0.21-31) 0.039 (0.21-31) 0.039 (0.21-31) 0.039 (0.21-32) 0.99 (0.21-32) 0.99 (0.21-32) 0.99 (0.21-32) 0.99 (0.21-32) 0.217 (0.70-1) 0.59 (0.51-139) 0.91 (0.21-31) 0.59 (0.52) (0.21-31) 0.59 (0.52) (0.21-31) 0.59 (0.52) (0.21-31) 0.59 (0.52) (0.21-31) 0.59 (0.52) (0.21-32) 0.210 (0.21-32) 0.210 (0.21-32) 0.2		Median (IQR)	0.56 (0.00-0.56)	0.7 (0.0016-1.4)	1.10 (1.05-1.14)	< 0.0001	1.07 (1.03-1.12)	0.001
	Days from disease onset	Mean (SD)	6.4 (6.9)	7.4 (6.4)				
Simplify bistory Current/past number 57 (33,93) 158 (43,13) 1.19 (034-1.5) 0.1474 0.99 (0.75-1.28) 0.9142 Diraking alcohol Yes 8 (0.63) 2.0,33) 0.04 (0.27-1.1) 0.510 0.753 0.11 (0.87-1.11) 0.142 0.99 (0.75-1.28) 0.973 0.974 0.99 (0.23-3.45) 0.9929 0.971 0.073 0.971 0.973 0.971 0.973 0.971 0.973 0.971 0.973 0.971 0.973 0.971 0.973 0.971 0.973 0.971 0.973 0.971 0.973 0.971 0.973 0.971 0.973 0.971 0.973 0.971 0.973 0.971 0.973 0.		Median (IQR)	6 (3-9)	7 (4, 9.5)	1.02 (1.00-1.04)	0.0297	1.01 (1-1.03)	0.1136
Drinking atcohol Ves 858 (653) 247 (67.38) 1.11 (0.87-1.41) 0.04148 0.96 (0.73-1.26) 0.7593 Myocardial Infratrion Ves 44 (3.23) 10 (2.73) 0.94 (0.2-4.45) 0.0592	Smoking history	Current/past smoker	537 (38.9%)	158 (43.1%)	1.19 (0.94-1.5)	0.1474	0.99 (0.76-1.28)	0.9142
	Drinking alcohol	Yes	898 (65%)	247 (67.3%)	1.11 (0.87-1.41)	0.4148	0.96 (0.73-1.26)	0.7593
Congenitive heart failure Ves 44 (2.32) 10 (2.73) 0.85 (0.42-1.71) 0.5502 infarction/congenitive Ves 49 (3.53) 12 (3.33) 0.52 (0.48-1.75) 0.7962 0.72 (0.35-1.42) 0.3333 infarction/congenitive Ves 11 (0.83) 41 (1.13) 1.37 (0.43-4.34) 0.5594 0.99 (0.22-3.45) 0.99029 Cerebrowscale disease Ves 16 (1.23) 41 (1.15) 0.95 (0.32-1.41) 0.570 (0.32-3.42) 0.6409 Dementa Ves 11 (35) 19 (5.23) 0.05 (0.3-1.03) 0.520 (0.3-0.31) 0.0501 Chronic lung disease Ves 51 (3.53) 10 (5.73) 0.9653 - - Pronchial asthma Ves 80 (5.83) 15 (4.13) 0.69 (0.39-1.22) 0.020 0.027 (0.4-1.41) 0.8896 disease/bronchial sathma -	Myocardial infarction	Yes	8 (0.6%)	2 (0.5%)	0.94 (0.2-4.45)	0.9393	. ,	
Mycardial infartcino(registive hart failure Yes 49 (3.5x) 12 (3.3x) 0.92 (0.48-1.75) 0.7962 0.72 (0.36-1.42) 0.3333 Peripheral vacular disease Vers Yes 11 (0.8x) 4 (1.1x) 1.37 (0.43-4.34) 0.5894 0.599 (0.29-3.45) 0.9025 Cerebroxecular disease Vers Yes 16 (1.2x) 4 (1.1x) 0.94 (0.31-2.83) 0.941 1.05 (0.32-3.42) 0.9490 Dementia Yes 11 (1.8x) 19 (5.2x) 0.62 (0.38-1.13) 0.656 0.52 (0.3-0.51) 0.0217 CDPD Yes 42 (3.3) 11 (3.3) 0.960 (0.39-1.20) 0.0263 0.777 1.7 (0.67-1.41) 0.889 (excluding CDPD) Yes 80 (5.83) 15 (4.18) 0.050 (0.39-1.20) 0.0271 0.7877 0.977 (0.67-1.41) 0.889 Midi Iver disease Yes 2 (0.13) 2 (0.53) 3.78 (0.53-6.51) 0.144 1.143 0.462 (0.32-1.20) 0.7877 0.977 (0.57-1.41) 0.889 Midi Iver disease Yes 2 (0.153) 13 (3.58) 1.06 (0.54-2.10) 0.851	Congestive heart failure	Yes	44 (3.2%)	10 (2.7%)	0.85 (0.42-1.71)	0.6502		
Infarction/congestive Ves 11 (0.83) 4 (1.13) 1.37 (0.43-4.34) 0.5894 0.99 (0.29-3.45) 0.9329 Peripheral vacular disease Ves 16 (1.23) 4 (1.13) 1.37 (0.43-4.34) 0.5894 0.99 (0.29-3.45) 0.9329 Paralysis Ves 16 (1.23) 4 (1.13) 0.94 (0.31-2.33) 0.914 1.05 (0.32-3.42) 0.9409 Dementia Ves 57 (4.13) 12 (5.23) 0.62 (0.38-1.03) 0.9653 0.921 (0.37-3.42) 0.9023 COPD Ves 57 (4.13) 20 (5.42) 1.05 (0.32-4.21) 0.0217 0.9053 Corbit/chronic ling Ves 80 (5.83) 15 (4.13) 0.66 (0.39-1.22) 0.2029 0.077 (0.67-1.41) 0.889 disease/pronchal astma Mila liver disease Yes 2 (0.13) 2 (0.53) 3.78 (0.53-2.631) 0.145 dystar Midal liver disease Yes 3 (2.83) 13 (3.53) 1.2 (0.64-2.64) -0.0001 1.4 (31.13) 2.27 (1.74-2.64) 0.0011 1.4 (3.14) 1.4 (3.14) 1.6 (1.12,-2.18)	Myocardial	Yes	49 (3.5%)	12 (3.3%)	0.92 (0.48-1.75)	0.7962	0.72 (0.36-1.42)	0.3393
hear failure Ves 11 (0.8X) 4 (1.1X) 1.37 (0.43-4.34) 0.5894 0.99 (0.29-3.45) 0.9920 Cerebroxacular diseas Ves 67 (4.9X) 19 (5.2X) 1.07 (0.51-181) 0.7777 1.1 (0.61-197) 0.7599 Paralysis Ves 111 (18X) 19 (5.2X) 0.62 (0.38-103) 0.0656 0.52 (0.3-0.51) 0.0217 COPD Ves 57 (4.1X) 20 (5.4X) 1.34 (0.79-2.26) 0.279 0.52 (0.3-0.51) 0.0217 COPD Ves 80 (5.8X) 15 (4.1X) 0.69 (0.59-1.23) 0.9653 0.52 (0.3-0.51) 0.8596 CCPOP(chronic ling Ves 10 (5 (7.4) 0.75 (0.57-1.41) 0.889 0.8596 0.573 0.97 (0.67-1.41) 0.889 disease/bronchial asthma 11 (32) 1.06 (0.54-2.1) 0.8596 0.573 0.99 (0.51-1.52) 0.9824 disease/moderate-to-sease/moderate-to-sease/moderate-to-sease/moderate-to-sease/moderate-to-sease/moderate-to-sease/moderate-to-sease/moderate-to-sease/moderate-to-sease/moderate-to-sease/moderate-to-sease/moderate-to-sease/moderate-to-sease/moderate-to-sease/moderate-to-sease/moderat-to-sease/moderate-to-sease/moderate-to-sease/mode	infarction/congestive				· · · ·			
Peripheral vascular disease Yes 11 (0.88) 4 (1.13) 1.37 (0.43-4.34) 0.5844 0.99 (0.25-3.45) 0.9282 Paralysis Yes 16 (1.23) 4 (1.13) 0.94 (0.31-2.31) 0.7777 1.1 (0.61-1.07) 0.7599 Paralysis Yes 111 (83) 19 (5.25) 0.62 (0.38-1.03) 0.0650 0.52 (0.3-0.91) 0.0217 COPD Yes 57 (4.13) 20 (5.41) 1.34 (0.79-2.26) 0.279 Corrol (ung discase / Yes 80 (5.83) 15 (4.13) 0.66 (0.39-1.20) 0.2029 (extuding COPD) Yes 80 (5.83) 15 (4.13) 0.66 (0.39-1.20) 0.2029 COPD/chronic lung Yes 166 (12.3) 46 (12.53) 1.06 (0.54-2.1) 0.8596	heart failure							
Cerebroaccular disease Yes 67 (4.97) 19 (5.2%) 1.07 (0.63.1-8.1) 0.9797 1.1 (0.61-1.97) 0.9340 Paralysis Yes 11 (1.8%) 19 (5.2%) 0.64 (0.13-2.8.3) 0.044 1.05 (0.32-3.42) 0.0320 Dementia Yes 57 (4.1%) 20 (5.4%) 1.34 (0.79-2.26) 0.625 (0.32-3.42) 0.0217 COPD Yes 57 (4.1%) 20 (5.4%) 1.34 (0.79-2.26) 0.625 (0.32-3.42) 0.0217 COPDIchonic lung disease Yes 40 (5.8%) 15 (4.1%) 0.99 (0.5-1.93) 0.9653 disease(Dronchial asthma Yes 16 (128) 46 (12.5%) 1.05 (0.74-1.4) 0.787 0.67 (0.16-1.4) 0.889 disease Yes 39 (2.8%) 11 (3%) 1.06 (0.54-2.1) 0.845 - - - - - - 0.67 (0.15-1.4) 0.67 (0.15-2.43) 0.5452 dysfunction Yes 2 (0.1%) 1 (0.5%) 0.75 (0.22-2.61) 0.6516 0.67 (0.19-2.43) 0.5452 dysfunction Yes 19 (1.2.	Peripheral vascular disease	Yes	11 (0.8%)	4 (1.1%)	1.37 (0.43-4.34)	0.5894	0.99 (0.29-3.45)	0.9929
	Cerebrovascular disease	Yes	67 (4.9%)	19 (5.2%)	1.07 (0.63-1.81)	0.7977	1.1 (0.61-1.97)	0.7599
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Paralysis	Yes	16 (1.2%)	4 (1.1%)	0.94 (0.31-2.83)	0.914	1.05(0.32 - 3.42)	0.9409
COPD Yes 57 (413) 20 (5.49) 1.34 (0.79-2.26) 0.2799 Late (1.417) Late (1.417) Chronic lung (OPD) Yes 42 (33) 11 (33) 0.99 (0.5-1.93) 0.96 (33 Brenchial astima Yes 80 (5.85) 15 (4.12) 0.65 (0.39-1.22) 0.2729 C////////////////////////////////////	Dementia	Yes	111 (8%)	19 (5.2%)	0.62(0.38 - 1.03)	0.0656	0.52 (0.3-0.91)	0.0217
$ \begin{array}{c c} \hline Chronic lung disease Yes 42 (33) 11 (33) 0.99 (0.5-1.93) 0.9653 \\ \hline Cexcluding (OPP) \\ \hline Bronchial asthma Yes 106 (123) 46 (12.3) 15 (4.13) 0.05 (0.39-1.22) 0.2029 \\ \hline Correct lung Yes 106 (123) 46 (12.3) 1.05 (0.39-1.22) 0.2029 \\ \hline COPD/chronic lung Yes 2 (0.18) 2 (0.53) 3.78 (0.53-26.91) 0.7887 0.57 (0.67-1.41) 0.889 \\ \hline Mid liver disease revere liver Yes 2 (0.18) 2 (0.53) 3.78 (0.53-26.91) 0.1845 \\ \hline Mid direct - severe liver Yes 2 (0.18) 2 (0.53) 3.78 (0.53-26.91) 0.1845 \\ \hline Mid direct - severe liver Yes 2 (0.18) 2 (0.53) 3.78 (0.53-26.91) 0.1845 \\ \hline Mid direct - severe liver Yes 2 (0.18) 2 (0.53) 3.78 (0.53-26.91) 0.1845 \\ \hline Mid direct - severe liver Yes 2 (0.18) 3 (0.85) 0.75 (0.22-2.61) 0.6516 0.657 (0.19-2.43) 0.5452 \\ \hline Myertenction Yes 15 (1.13) 3 (0.853) 0.75 (0.22-2.61) 0.6516 0.657 (0.19-2.43) 0.5452 \\ \hline Myertencion Yes 192 (28.48) 166 (45.23) 2.08 (1.64-2.64) -0.0001 1.48 (1.1-1.93) 0.0101 \\ \hline Hypertencion Yes 192 (28.48) 166 (45.23) 2.08 (1.64-2.64) -0.0001 1.48 (1.1-1.93) 0.0101 \\ \hline Myertencion Yes 192 (28.48) 166 (45.23) 2.08 (1.64-2.64) -0.0001 1.48 (1.1-1.93) 0.0101 \\ \hline Complications Yes 192 (28.48) 166 (45.23) 2.05 (1.12-3.73) 0.0192 \\ \hline Complications Yes 12 (2.03) 17 (4.63) 2.05 (1.12-3.73) 0.0192 \\ \hline Complications Yes 260 (18.39) 131 (35.78) 2.09 (1.63-3.08) -0.0001 1.65 (1.26-2.18) 0.0003 \\ \hline Complications Yes 90 (6.53) 43 (11.73) 1.9 (1.3-2.79) 0.001 1.55 (1.26-2.18) 0.0003 \\ \hline Complications Yes 90 (6.53) 43 (11.73) 1.9 (1.3-2.79) 0.001 1.28 (0.82-2.02) 0.2795 \\ \hline Diabetes (with e without Yes 260 (18.39) 15 (4.13) 1.07 (0.59-1.92) 0.8262 \\ \hline Metastatic solid tumour Yes 18 (1.33) 1.0 (0.73) 2 (0.55) 1.29 \\ \hline Medarate - severe renal Yes 10 (0.73) 2 (0.58) 1.03 (0.470-3.55) 0.4633 \\ \hline Moderate - severe renal Yes 10 (0.73) 2 (0.53) 1.6 (0.63-3.50) 0.926 0.82 (0.21-3.13) 0.6844 \\ \hline Myerter - severe renal Yes 12 (0.93) 3 (0.83) 15 (4.13) 1.07 (0.59-1.92) 0.3262 \\ \hline Metastatic solid tumour Yes 18 (1.432) 15 (4.13) 1.07 (0.59-1.92) 0.3262 \\ \hline Metastatic solid tumour Yes 18 (1.633) 1.$	COPD	Yes	57 (4.1%)	20 (5.4%)	1.34 (0.79–2.26)	0.2739		
(excluding COPD) Iter (b)	Chronic lung disease	Yes	42 (3%)	11 (3%)	0.99(0.5-1.93)	0.9653		
Bronchial asthma (COPD)chronic lung disease/ronchial asthma Yes 80 (5.8%) 166 (12%) 15 (4.1%) 46 (12.5%) 0.66 0 (0.39–1.22) 1.0 (0.74-1.49) 0.2029 Mide liver lisease dysfunction Yes 39 (2.8%) 11 (3%) 2 (0.5%) 1.06 (0.54-2.1) 3.78 (0.53-2.61) 0.8896 Mide liver disease dysfunction Yes 2 (0.1%) 2 (0.5%) 3.78 (0.53-2.61) 0.8976 Mide liver disease/moderate-to-severe liver dysfunction Yes 41 (3%) 13 (3.5%) 1.2 (0.64-2.26) 0.573 0.99 (0.51-1.92) 0.9824 Hypertension Yes 392 (2.84%) 166 (45.25%) 2.08 (1.64-2.64) <0.0001	(excluding COPD)	105	12 (3,0)	11 (5%)	0.55 (0.5 1.55)	0.5055		
COPD/chronic lung disease/monchial Yes 166 (12%) 46 (12.5%) 1.05 (0.74-1.49) 0.7887 0.97 (0.67-1.41) 0.889 Mid liver disease Moderate-to-severe liver dysfunction Yes 39 (2.8%) 11 (3%) 1.06 (0.54-2.1) 0.8596 Mid liver disease Moderate-to-severe liver dysfunction Yes 4 (13%) 13 (3.5%) 1.2 (0.64-2.26) 0.573 0.99 (0.51-1.92) 0.9824 Bisease/moderate-to- severe liver dysfunction Yes 35 (0.1%) 2 (0.5%) 2.08 (1.64-2.26) 0.6516 0.67 (0.19-2.43) 0.5452 Hypertension Yes 392 (28.4%) 166 (45.2%) 2.08 (1.64-2.64) <0.0001	Bronchial asthma	Ves	80 (5.8%)	15 (4 1%)	0.69 (0.39-1.22)	0 2029		
Construction Res Res< Res Res <	COPD/chronic lung	Vac	166 (12%)	15 (4.1%) 16 (12 5%)	1.05(0.74 - 1.49)	0.7887	0.07(0.67 - 1.41)	0 880
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$	disease/bronchial	105	100 (12%)	40 (12.5%)	1.05 (0.74-1.45)	0.7887	0.97 (0.07-1.41)	0.885
Moderate-to-severe liver Yes 2 (0.1%) 2 (0.5%) 3.78 (0.53-26.91) 0.1845 dysfunction Mild liver Yes 41 (3%) 13 (3.5%) 1.2 (0.64-2.26) 0.573 0.99 (0.51-1.92) 0.9824 severe liver disasse/moderate-to-severe Ves 15 (1.1%) 3 (0.8%) 0.75 (0.22-2.61) 0.6516 0.67 (0.19-2.43) 0.5452 Peptic ulcer Yes 139 (28.4%) 166 (45.2%) 2.08 (1.64-2.64) <0.0001	Mild liver disease	Ves	39 (2.8%)	11 (3%)	1.06(0.54-2.1)	0.8596		
$\begin{array}{ c c c c c c c c c c c c c c c c c c c$	Moderate-to-severe liver	Yes	2(0.1%)	2(0.5%)	3.78(0.53-26.91)	0.1845		
up of the two multiple Yes 41 (3%) 13 (3.5%) 1.2 (0.64-2.26) 0.573 0.99 (0.51-1.92) 0.9824 disease (moderate-to-sever liver dysfunction	dysfunction	105	2 (0.1%)	2 (0.5%)	5.70 (0.55 20.51)	0.1045		
Interf tree Test (1,3) Test (1,3) </td <td>Mild liver</td> <td>Ves</td> <td>41 (3%)</td> <td>13 (3 5%)</td> <td>1.2(0.64-2.26)</td> <td>0 573</td> <td>0.99(0.51 - 1.92)</td> <td>0 9824</td>	Mild liver	Ves	41 (3%)	13 (3 5%)	1.2(0.64-2.26)	0 573	0.99(0.51 - 1.92)	0 9824
sever liver dysfunction Peptic ulcer Yes 15 (1.1%) 3 (0.8%) 0.75 (0.22–2.61) 0.6516 0.67 (0.19–2.43) 0.5452 Hyperension Yes 392 (28.4%) 166 (45.2%) 2.08 (1.64–2.64) <0.0001 1.48 (1.1–1.99) 0.0101 Hyperlipidemia Yes 229 (16.6%) 114 (31.1%) 2.27 (1.74–2.95) <0.0001 Complications Diabetes without Yes 229 (16.6%) 114 (31.1%) 2.27 (1.74–2.95) <0.0001 Diabetes without Yes 229 (16.6%) 114 (31.1%) 2.27 (1.74–2.95) <0.0001 Complications Diabetes with Yes 32 (2.3%) 17 (4.6%) 2.05 (1.12–3.73) 0.0192 Complications Diabetes with Yes 90 (6.5%) 43 (11.7%) 1.9 (1.3–2.79) 0.001 1.65 (1.26–2.18) 0.0003 complications Diabetes (with or without Yes 90 (6.5%) 43 (11.7%) 1.9 (1.3–2.79) 0.001 1.28 (0.82–2.02) 0.2795 diagnosis Moderate-to-severe renal Yes 10 (0.7%) 2 (0.5%) 0.75 (0.16–3.44) 0.7129 Haemodialysis before Yes 4 (0.3%) 2 (0.5%) 1.89 (0.34–10.35) 0.4633 admission Moderate-to-severe renal Yes 12 (0.9%) 3 (0.8%) 0.94 (0.26–3.35) 0.9256 0.82 (0.21–3.13) 0.7684 dysfunc- tion/haemodialysis before admission Solid tumour Yes 13 (3.8%) 15 (4.1%) 1.07 (0.59–1.92) 0.8262 Metastatic solid tumour Yes 18 (1.3%) 1 (0.3%) 0.21 (0.03–1.55) 0.1258 Solid tumour Leukaemia Yes 3 (0.2%) 1 (0.3%) 0.21 (0.03–1.55) 0.1258 Solid tumour Leukaemia Yes 3 (0.2%) 1 (0.3%) 0.21 (0.03–1.55) 0.1258 Solid tumour Leukaemia Yes 3 (0.2%) 1 (0.3%) 0.21 (0.03–1.55) 0.1258 Solid tumour Leukaemia Yes 3 (0.2%) 1 (0.3%) 0.47 (0.06–3.39) 0.338 1.66 (0.58–4.73) 0.3037 Solid tumour Leukaemia Yes 11 (0.8%) 2 (0.5%) 0.68 (0.15–3.09) 0.6206 0.73 (0.5–3.51) 0.6954 Collagen disease Yes 15 (1.1%) 6 (1.6%) 1.51 (0.58–3.39) 0.338 1.66 (0.58–4.73) 0.3418 Limunuosuppression Yes 39 (2.8%) 12 (3.3%) 1.16 (0.6–2.24) 0.6523 1.18 (0.56–2.51) 0.658 ACEI Yes 23 (1.7%) 11 (3%) 1.82 (0.88–3.78) 0.1055 1.45 (0.68–3.08) 0.3407 ARB Yes 198 (1.4.3%) 8 (2.32.2%) 1.83 (1.35–1.45 (0.68–3.08) 0.3407	disease/moderate-to-	105	11 (3,6)	13 (3.3%)	1.2 (0.01 2.20)	0.575	0.55 (0.51 1.52)	0.5021
dysfunction Preptic ulcer Yes 15 (1.1%) 3 (0.8%) 0.75 (0.22-2.61) 0.6516 0.67 (0.19-2.43) 0.5452 Hypertension Yes 392 (28.4%) 166 (45.2%) 2.08 (1.64-2.64) <0.0001	severe liver							
Opsilization Performan Ves 15 (1.1%) 3 (0.8%) 0.75 (0.22-2.61) 0.6516 0.67 (0.19-2.43) 0.5452 Hypertension Yes 392 (28.4%) 166 (45.2%) 2.08 (1.64-2.64) -0.0001 1.48 (1.1-1.99) 0.0101 Hypertiphidemia Yes 229 (16.6%) 114 (31.1%) 2.27 (1.74-2.95) <0.0001	dysfunction							
Input duct Instruct Instruct <thinstruct< th=""> Instruct <t< td=""><td>Pentic ulcer</td><td>Ves</td><td>15 (1 1%)</td><td>3 (0.8%)</td><td>0.75(0.22-2.61)</td><td>0.6516</td><td>0.67(0.19-2.43)</td><td>0 5452</td></t<></thinstruct<>	Pentic ulcer	Ves	15 (1 1%)	3 (0.8%)	0.75(0.22-2.61)	0.6516	0.67(0.19-2.43)	0 5452
Hyperificiation Hts 352 (26.4%) Ho0 (12.4%) 20.0 (1.34-2.4%) C0.001 Ho0 (1.11.52) 0.0101 Hyperificiations 229 (16.6%) 114 (31.1%) 2.27 (1.74-2.95) <0.0001	Hypertension	Vec	302 (28 4%)	166 (45.2%)	2.08(1.64-2.64)	~0.001	1/18 (11-100)	0.0402
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Hypertension	Voc	174(12.6%)	69 (19 5%)	2.00(1.04-2.04) 1.59(1.16, 2.15)	0.0026	1.40(1.1-1.55) 1.01(0.71, 1.42)	0.0762
Diabetes without res 229 (16.84) 114 (31.14) 2.27 (1.74-2.95) <0.0001 complications	Dishotos without	Ves	174(12.0%)	114(2119)	1.30(1.10-2.13)	0.0030	1.01 (0.71-1.42)	0.9703
Completations Ves 32 (2.3%) 17 (4.6%) 2.05 (1.12-3.73) 0.0192 Diabetes with or without complications Ves 260 (18.8%) 131 (35.7%) 2.39 (1.86-3.08) <0.0001		ies	229 (10.0%)	114 (51.1%)	2.27 (1.74-2.95)	<0.0001		
Diabetes with complications Part (4.0.8) 2.05 (1.12–3.7.3) 0.0132 Diabetes (with or without complications) Yes 260 (18.8%) 131 (35.7%) 2.39 (1.86–3.08) <0.0001	Diabotos with	Voc	22(22%)	17 (16%)	205(112272)	0.0102		
Diabetes (with or without complications) Yes 260 (18.8%) 131 (35.7%) 2.39 (1.86-3.08) <0.0001 1.65 (1.26-2.18) 0.0003 Obesity (physicians' diagnosis) Yes 90 (6.5%) 43 (11.7%) 1.9 (1.3-2.79) 0.001 1.28 (0.82-2.02) 0.2795 diagnosis) Moderate-to-severe renal dysfunction Yes 10 (0.7%) 2 (0.5%) 0.75 (0.16-3.44) 0.7129	complications	105	52 (2.5%)	17 (4.0%)	2.03 (1.12-3.73)	0.0192		
Diabetes (with of without field 200 (18.5k) 131 (35.7k) 2.39 (1.80-3.08) <0.0001	Diabatas (with or without	Voc	260 (19.9%)	121 (25 7%)	2 20 (1 96 2 09)	-0.0001	165 (126 219)	0.0002
Obesity (physicians' diagnosis) Yes 90 (6.5%) 43 (11.7%) 1.9 (1.3–2.79) 0.001 1.28 (0.82–2.02) 0.2795 Moderate-to-severe renal dysfunction Yes 10 (0.7%) 2 (0.5%) 0.75 (0.16–3.44) 0.7129	Diabetes (with of without	ies	200 (18.8%)	151 (55.7%)	2.59 (1.60-5.06)	<0.0001	1.05 (1.20-2.16)	0.0005
Obesity (physicality of physicality of the second secon	Obasity (nhusisians)	Vee	00 (6 5%)	42 (11 79/)	10(12 270)	0.001	1 20 (0.02 2.02)	0.2705
Indentions/ Moderate-to-severe renal dysfunction Yes 10 (0.7%) 2 (0.5%) 0.75 (0.16-3.44) 0.7129 Haemodialysis before admission Yes 4 (0.3%) 2 (0.5%) 1.89 (0.34-10.35) 0.4633 Moderate-to-severe renal dysfunc- tion/haemodialysis before admission Yes 12 (0.9%) 3 (0.8%) 0.94 (0.26-3.35) 0.9256 0.82 (0.21-3.13) 0.7684 Moderate-to-severe renal dysfunc- tion/haemodialysis before admission Yes 53 (3.8%) 15 (4.1%) 1.07 (0.59-1.92) 0.8262 Solid tumour Yes 53 (3.8%) 15 (4.1%) 1.07 (0.59-1.92) 0.8262 Metastatic solid tumour Yes 18 (1.3%) 1 (0.3%) 0.21 (0.03-1.55) 0.1258 Solid tumour/metastatic Yes 70 (5.1%) 16 (4.4%) 0.85 (0.49-1.49) 0.577 0.73 (0.4-1.33) 0.3037 solid tumour Yes 3 (0.2%) 1 (0.3%) 0.26 (0.13-12.1) 0.8442 Umphoma Leukaemia Yes 3 (0.2%) 1 (0.3%) 0.47 (0.06-3.76) 0.4759 Leukaemia/lymphoma Yes 10 (0.8%)<	diamonia)	res	90 (6.5%)	43 (11.7%)	1.9 (1.3–2.79)	0.001	1.28 (0.82-2.02)	0.2795
Moderate-to-severe renal dysfunction Yes 10 (0.7k) 2 (0.5k) 0.75 (0.16–3.44) 0.7129 Haemodialysis before admission Yes 4 (0.3%) 2 (0.5%) 1.89 (0.34–10.35) 0.4633 Moderate-to-severe renal dysfunc- tion/haemodialysis before admission Yes 12 (0.9%) 3 (0.8%) 0.94 (0.26–3.35) 0.9256 0.82 (0.21–3.13) 0.7684 Moderate-to-severe renal dysfunc- tion/haemodialysis before admission Yes 53 (3.8%) 15 (4.1%) 1.07 (0.59–1.92) 0.8262 Metastatic solid tumour solid tumour solid tumour fumour/metastatic Yes 18 (1.3%) 1 (0.3%) 0.21 (0.03–1.55) 0.1258 Solid tumour solid tumour Leukaemia Yes 3 (0.2%) 1 (0.3%) 0.26 (0.13–1.2.1) 0.8442 Lymphoma Yes 3 (0.2%) 1 (0.3%) 0.47 (0.06–3.76) 0.4759 Leukaemia/lymphoma Yes 10 (0.8%) 2 (0.5%) 0.68 (0.15–3.09) 0.6206 0.73 (0.15–3.51) 0.6954 Collagen disease Yes 15 (1.1%) 6 (1.6%) 1.51 (0.58–3.93) 0.3938 1.66 (0.58–4.73) 0.3418 Immunosuppression Yes 39 (2.8%) 12 (3.3%)	diagnosis)	V	10 (0.7%)	2 (0 5%)	0.75 (0.16, 0.44)	0.7100		
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Solid tumour/metastatic solid tumour Yes 70 (5.1%) 16 (4.4%) 0.85 (0.49–1.49) 0.577 0.73 (0.4–1.33) 0.3037 Leukaemia Lymphoma Yes 3 (0.2%) 1 (0.3%) 1.26 (0.13–12.1) 0.8442 Leukaemia/lymphoma Yes 8 (0.6%) 1 (0.3%) 0.47 (0.06–3.76) 0.4759 Leukaemia/lymphoma Yes 11 (0.8%) 2 (0.5%) 0.68 (0.15–3.09) 0.6206 0.73 (0.15–3.51) 0.6954 Collagen disease Yes 15 (1.1%) 6 (1.6%) 1.51 (0.58–3.93) 0.3938 1.66 (0.58–4.73) 0.3418 Immunosuppression Yes 39 (2.8%) 12 (3.3%) 1.16 (0.6–2.24) 0.6523 1.18 (0.56–2.51) 0.658 ACEI Yes 198 (14.3%) 85 (23.2%) 1.8 (1.35–2.4) <0.0001	Metastatic solid tumour	Yes	18 (1.3%)	1 (0.3%)	0.21 (0.03-1.55)	0.1258		
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LeukaemiaYes3 (0.2%)1 (0.3%)1.26 (0.13-12.1)0.8442LymphomaYes8 (0.6%)1 (0.3%)0.47 (0.06-3.76)0.4759Leukaemia/lymphomaYes11 (0.8%)2 (0.5%)0.68 (0.15-3.09)0.6200.73 (0.15-3.51)0.6954Collagen diseaseYes15 (1.1%)6 (1.6%)1.51 (0.58-3.93)0.39381.66 (0.58-4.73)0.3418ImmunosuppressionYes39 (2.8%)12 (3.3%)1.16 (0.6-2.24)0.65231.18 (0.56-2.51)0.658ACEIYes198 (14.3%)85 (23.2%)1.8 (1.35-2.4)<0.001	solid tumour							
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Leukaemia/lymphomaYes11 (0.8%)2 (0.5%)0.68 (0.15-3.09)0.62060.73 (0.15-3.51)0.6954Collagen diseaseYes15 (1.1%)6 (1.6%)1.51 (0.58-3.93)0.39381.66 (0.58-4.73)0.3418ImmunosuppressionYes39 (2.8%)12 (3.3%)1.16 (0.6-2.24)0.65231.18 (0.56-2.51)0.658ACEIYes23 (1.7%)11 (3%)1.82 (0.88-3.78)0.10551.45 (0.68-3.08)0.3407ARBYes198 (14.3%)85 (23.2%)1.8 (1.35-2.4)<0.001	Lymphoma	Yes	8 (0.6%)	1 (0.3%)	0.47 (0.06-3.76)	0.4759		
Collagen diseaseYes15 (1.1%)6 (1.6%)1.51 (0.58-3.93)0.39381.66 (0.58-4.73)0.3418ImmunosuppressionYes39 (2.8%)12 (3.3%)1.16 (0.6-2.24)0.65231.18 (0.56-2.51)0.658ACEIYes23 (1.7%)11 (3%)1.82 (0.88-3.78)0.10551.45 (0.68-3.08)0.3407ARBYes198 (14.3%)85 (23.2%)1.8 (1.35-2.4)<0.0001	Leukaemia/lymphoma	Yes	11 (0.8%)	2 (0.5%)	0.68 (0.15-3.09)	0.6206	0.73 (0.15-3.51)	0.6954
ImmunosuppressionYes39 (2.8%)12 (3.3%)1.16 (0.6–2.24)0.65231.18 (0.56–2.51)0.658ACEIYes23 (1.7%)11 (3%)1.82 (0.88–3.78)0.10551.45 (0.68–3.08)0.3407ARBYes198 (14.3%)85 (23.2%)1.8 (1.35–2.4)<0.0001	Collagen disease	Yes	15 (1.1%)	6 (1.6%)	1.51 (0.58-3.93)	0.3938	1.66 (0.58-4.73)	0.3418
ACEI Yes 23 (1.7%) 11 (3%) 1.82 (0.88-3.78) 0.1055 1.45 (0.68-3.08) 0.3407 ARB Yes 198 (14.3%) 85 (23.2%) 1.8 (1.35-2.4) <0.0001	Immunosuppression	Yes	39 (2.8%)	12 (3.3%)	1.16 (0.6-2.24)	0.6523	1.18 (0.56-2.51)	0.658
ARB Yes 198 (14.3%) 85 (23.2%) 1.8 (1.35-2.4) <0.0001 0.99 (0.7-1.4) 0.961	ACEI	Yes	23 (1.7%)	11 (3%)	1.82 (0.88-3.78)	0.1055	1.45 (0.68-3.08)	0.3407
	ARB	Yes	198 (14.3%)	85 (23.2%)	1.8 (1.35–2.4)	< 0.0001	0.99 (0.7-1.4)	0.961

SD, standard deviation; IQR, interquartile range; OR, odds ratio; CI, confidence interval; BMI, body mass index; COPD, chronic obstructive pulmonary disease; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker. ^a Chi-squared test between the treatment and no treatment groups.



Figure 1. Survival probability by day 29 in patients who did and did not receive anticoagulation therapy during hospitalization. The results are presented for the following three groups: whole cohort (a); patients who did not receive steroids (b); and patients who received steroids (c).

Table 2

Comparison of 29-day mortality between patients who received and those who did not receive anticoagulation treatment.

	Survivor Crude cohort		Survivor Crude cohort		Non-si	urvivor	Total number	HR ^a	95% CI	P-value	aHR ^b	95% CI	P-value
Whole cohort	1616	92.40%	132	7.60%	1748								
No treatment	1290	93.4%	91	6.6%	1381								
Treatment	326	88.8%	41	11.2%	367	1.25	(0.86-1.81)	0.242	1.02	(0.80-1.29)	0.99		
No steroid therapy	1150	94%	73	6%	1223								
No treatment	1029	94.8%	56	5.2%	1085								
Treatment	121	87.7%	17	12.3%	138	1.62	(0.94 - 2.79)	0.084	1.31	(0.97 - 1.78)	0.082		
Steroid therapy	466	88.80%	59	11.20%	525								
No treatment	261	88.2%	35	11.8%	296								
Treatment	205	89.5%	24	10.5%	229	0.76	(0.45-1.29)	0.311	0.72	(0.50-1.03)	0.075		

HR, hazard ratio; aHR, adjusted hazard ratio; CI, confidence interval; IPTW, inverse probability of treatment weight.

^a HR for mortality in the treatment group compared with that in the no treatment group.

^b IPTW-aHR.

tended to be lower from approximately 1 week after admission compared with that in the anticoagulant group; this trend continued until day 29.

Table 2 shows a comparison of 29-day mortality between patients who received anticoagulation therapy and patients who did not receive anticoagulation therapy. In the whole cohort, the hazard ratio (HR) for 29-day mortality was slightly higher in the anticoagulant group than in the non-anticoagulant group, without any significant difference observed [HR 1.25; 95% confidence interval (CI) 0.86-1.81; P=0.242]. The IPTW-adjusted HR was 1.02 (95% CI 0.80-1.29; P=0.99). In patients who did not receive steroids, the crude and adjusted HRs were 1.62 (95% CI 0.94-2.79; P=0.084) and 1.31 (95% CI 0.97-1.78; P=0.082), respectively. In patients who received steroids, the crude and adjusted HRs were 0.76 (95% CI 0.45-1.29; P=0.311) and 0.72 (95% CI 0.5-1.03; P=0.075), respectively. When the interaction effect of steroid treatment and anticoagulation was included in the model, a P-value of 0.008 was observed, suggesting that the drug effect was different between patients who received and did not receive steroids. The missing data were complemented with the MCMC method of multiple imputation, and sensitivity analysis was performed. Interestingly, there was almost no difference in the results [adjusted HR or whole cohort: 1.00 (95% CI 0.79–1.27; P=1.00); no steroid therapy: 1.34 (95% CI 0.99–1.82; *P*=0.057); steroid therapy: 0.71 (95% CI 0.49–1.02; P=0.060]. Table S1 (see online supplementary material) summarizes the distribution of PS. There was no extreme weighting by PS, and the IPTW method was considered acceptable.

The characteristics of patients with or without anticoagulation treatment during hospitalization in the weighted population were analysed further. The results are presented in Table S2 (see online supplementary material). Insufficient adjustment for age and dementia was observed. Therefore, in addition to the IPTW analysis, another analysis was performed in which age and dementia were directly included in the Cox proportional hazard model.

The adjusted HRs were as follows: whole cohort: 1.18 (95% CI 0.94–1.50; *P*=0.16); no steroid therapy: 1.62 (95% CI 1.19–2.20; *P*=0.0023); and steroid therapy: 0.78 (95% CI 0.54–1.11; *P*=0.17).

Table 3 shows the complications during hospitalization in patients who received anticoagulation therapy and patients who did not receive anticoagulation therapy. Overall, complications were more frequently observed in the anticoagulant group than in the non-anticoagulant group.

Discussion

To the best of the authors' knowledge, this is the largest study to evaluate the efficacy of anticoagulants in reducing mortality in patients hospitalized for COVID-19 in Japan. After PS IPTW adjustment, no clear effect of anticoagulant use or non-use on mortality was found in the entire cohort; however, a trend towards lower mortality in the steroid use group was identified.

Past studies on the use of anticoagulants in other countries have reported their effectiveness against severe illness and death in hospitalized patients with COVID-19 (Rentsch et al., 2019; Hanif et al., 2020; Nadkarni et al., 2020). In the present study, the trend towards anticoagulation benefit was found in the steroid use group alone, which may be attributed to several reasons. First, in most previous studies, anticoagulation therapy was initiated 24–48 h after admission (Rentsch et al., 2019; Nadkarni et al., 2020). Unfortunately, COVIREGI-JP does not collect data concerning the timing of anticoagulation therapy initiation or the length of treatment. In addition, the treatment may have been interrupted. Although patients who were critically ill on admission were not included in this study, it is possible that the study included a population in whom anticoagulation therapy was initiated too late. Notably, there

Table	3
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Anticoagulation treatment and respiratory support^a during hospitalization.

	No oxygen		Oxygen		IMV/ECMO		Total number	
Whole cohort	494	28.30%	943	54%	310	17.70%	1747	
No treatment	479	34.7%	771	55.9%	130	9.4%	1380	
Treatment	15	4.1%	172	46.9%	180	49.0%	367	
No steroid therapy	459	37.6%	621	50.8%	142	11.6%	1222	
No treatment	452	41.7%	555	51.2%	77	7.1%	1084	
Treatment	7	5.1%	66	47.8%	65	47.1%	138	
Steroid therapy	35	6.7%	322	61.3%	168	32.0%	525	
No treatment	27	9.1%	216	73.0%	53	17.9%	296	
Treatment	8	3.5%	106	46.3%	115	50.2%	229	

IMV/ECMO, invasive mechanical ventilation/extracorporeal membrane oxygenation.

^a Definitions are as reported previously (Matsunaga et al., 2020).

Table 4

Complications during hospitalization in patients with or without anticoagulation therapy.

	No treatment (<i>n</i> =1381)	Treatment $(n=367)$
ARDS	108 (7.8%)	149 (40.6%)
Cerebral infarction or hemorrhage	5 (0.4%)	4 (1.1%)
Bloody sputum/haemoptysis	16 (1.2%)	5 (1.4%)
Deep vein thrombosis	2 (0.1%)	19 (5.2%)
Myocardial ischaemia	2 (0.1%)	5 (1.4%)
Gastrointestinal bleeding	13 (0.9%)	8 (2.2%)
Pulmonary thromboembolism	1 (0.1%)	8 (2.2%)

ARDS, acute respiratory distress syndrome.

were significantly more patients in the anticoagulant group on invasive mechanical ventilation/extracorporeal membrane oxygenation (IMV/ECMO) during hospitalization compared with the nonanticoagulant group (49% vs 9.4%), indicating a higher number of critically ill patients in the anticoagulant group. As the PS used for adjustment was based on factors at the time of admission (e.g. patient background, D-dimer, etc.), it is possible that it was not entirely accurate as it did not account for other conditions, including severity of illness at the time of anticoagulant initiation.

Second, this study may not have found a benefit for the whole cohort because the included patients with COVID-19 had fewer thrombotic events, comorbidities associated with severe disease, and severity of disease compared with other studies. The median D-dimer level at admission in the study participants was lower than that reported in a previous study (Nadkarni et al., 2020). There were few episodes of deep vein thrombosis and pulmonary embolism in the present study, although they may have been under-reported. Overall, 28% of patients did not receive oxygen during hospitalization, and although the mortality rate in the anticoagulant group was similar to that reported in a previous study (Rentsch et al., 2019), the corresponding rate in the nonanticoagulant group was considerably lower than reported previously (Rentsch et al., 2019; Nadkarni et al., 2020). The frequency of comorbidities (such as diabetes and high BMI) that can lead to serious illness was also lower in the present study compared with previous cohort studies (Rentsch et al., 2019; Nadkarni et al., 2020).

Since June 2020, steroids have been used actively in Japan to reduce mortality (Horby et al., 2021). This study was novel in that the use of steroids was not included in the PS model, but was analysed in a stratified manner to assess the benefit of anticoagulation more accurately. In patients who did not receive steroids, the non-anticoagulant group included many mildly ill patients (i.e. more than 40% did not use oxygen), which may have contributed to the failure to prove the efficacy of anticoagulants in patients in this stratum or in the whole cohort (including patients in this stratum).

The steroid population, which included more severely ill patients compared with the overall cohort, still had a higher rate of IMV/ECMO use in the anticoagulant group than in the nonanticoagulant group; however, the difference was narrowed compared with that in the whole cohort. Assuming that all the patients who died in this study cohort were treated with IMV/ECMO, the fatality rates among intubated patients would be as follows: patients who received steroids [56/77 (72.7%) in the nonanticoagulant group; 17/65 (26.2%) in the anticoagulant group] and patients who did not receive steroids [35/53 (67.9%) in the nonanticoagulant group; 24/115 (67.9%) in the anticoagulant group]. Notably, more patients (62.1%) in the steroid use group were enrolled in COVIREGI-JP after June 2020 than patients in the nonsteroid use group (35.2%). As novel evidence of COVID-19 emerges over time, it is necessary to consider the impact of improved management other than steroid use. This point may, at least in part, explain the finding that the IPTW-adjusted HR, adjusting age and dementia by including those in the Cox model, showed that anticoagulation therapy may have been more harmful to the patients who did not receive steroid therapy.

The involvement of thrombosis in the severity of COVID-19 has been highlighted since the early stages of the pandemic, and an algorithm for anticoagulation was issued by Mount Sinai Hospital in April 2020 (Mount Sinai Health System, 2021). While direct oral anticoagulants (DOACs) have been used in other countries, not all DOACs have been approved for thromboprophylaxis in Japan. The use of warfarin is also considered suboptimal because of the difficulty in controlling thrombosis. Although the authors issued a recommendation for the subcutaneous administration of unfractionated heparin or low-molecular-weight heparin for hospitalized patients (Sato et al., 2020), this occurred later than the recommendations in overseas reports; therefore, the use of anticoagulants did not become a standard practice in Japan immediately. The rate of anticoagulant use was low in the present study cohort [367/1748 (21%)] of hospitalized patients with COVID-19.

In addition to the points discussed thus far, there are several caveats to the interpretation of the results of this study. As this was an observational study using registry data, it is subject to limitations as described previously (Matsunaga et al., 2020), such as bias from the overall inpatient population in Japan and future data updates. Although the COVIREGI-JP data provided information on the indications for anticoagulant use (e.g. therapeutic or prophy-

lactic), there were cases in which it was difficult to make a strict distinction because the doses of anticoagulants were not collected. Therefore, the authors did not distinguish between the two. This is an area where there is still insufficient evidence on the appropriate target population, and the superiority of prophylactic or therapeutic dosing (National Institutes of Health 2021b; Sadeghipour et al., 2021).

In conclusion, this study found that anticoagulation therapy tended to reduce 29-day mortality in hospitalized patients with COVID-19 in Japan who were also treated with steroids. These results suggest that anticoagulants would be beneficial in Asians, in whom comorbidities and risk of thrombosis may differ from other ethnic groups, and provide a rationale for promoting anticoagulation therapy in hospitalized patients in Asian countries, including Japan. Further studies are needed to determine the appropriate target population and treatment initiation.

Declaration of Competing Interest

H. Ohtsu reports personal fees as a statistician and as an external consultant for clinical trials from EPS International, outside the submitted work. S. Saito reports grants from Shionogi, outside the submitted work. The other authors report no conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2021.09.014.

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